A.M.A. Archives of
OPHTHALMOLOGY

DECEMBER 1956

VOLUME 56 NUMBER 6

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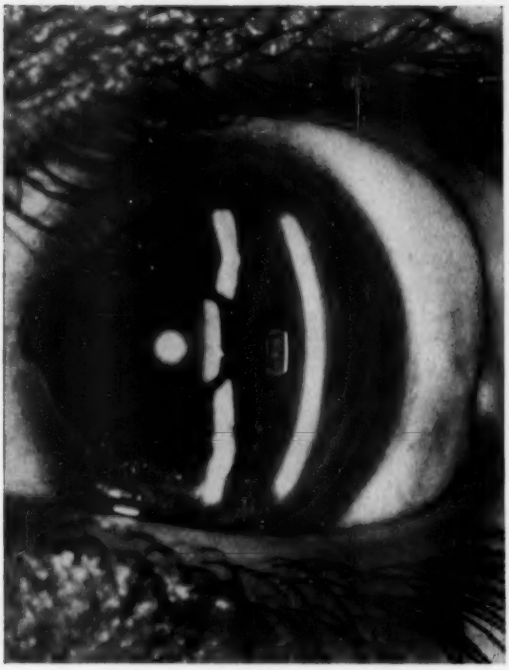

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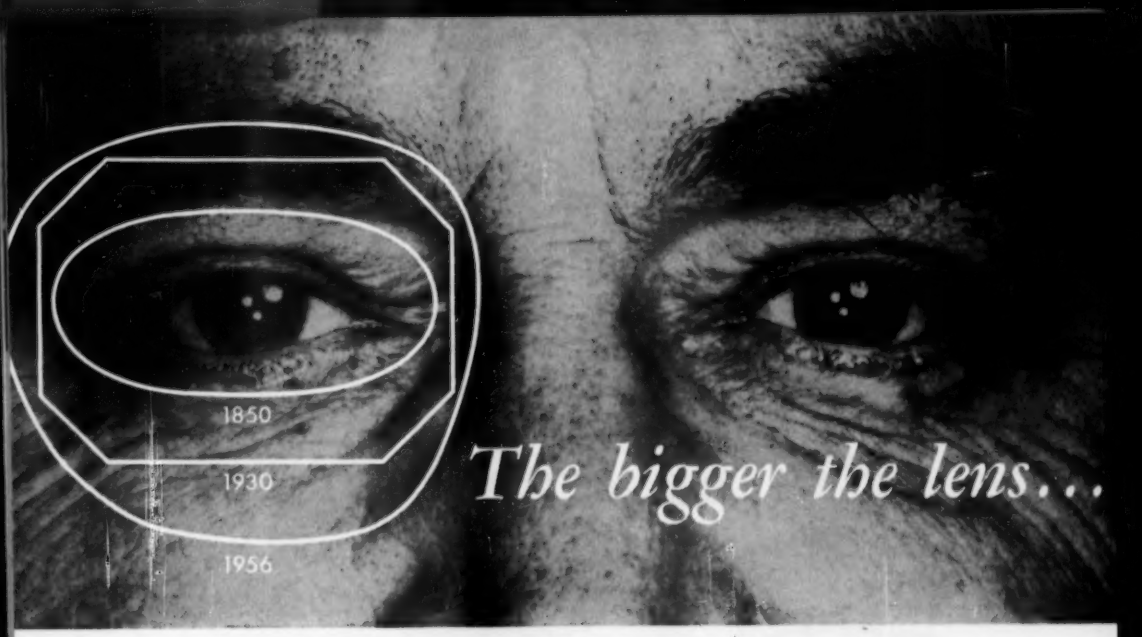

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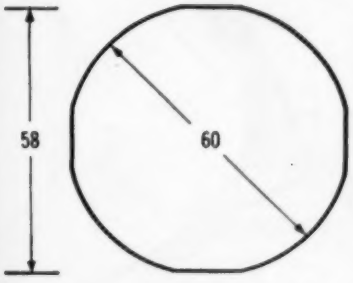

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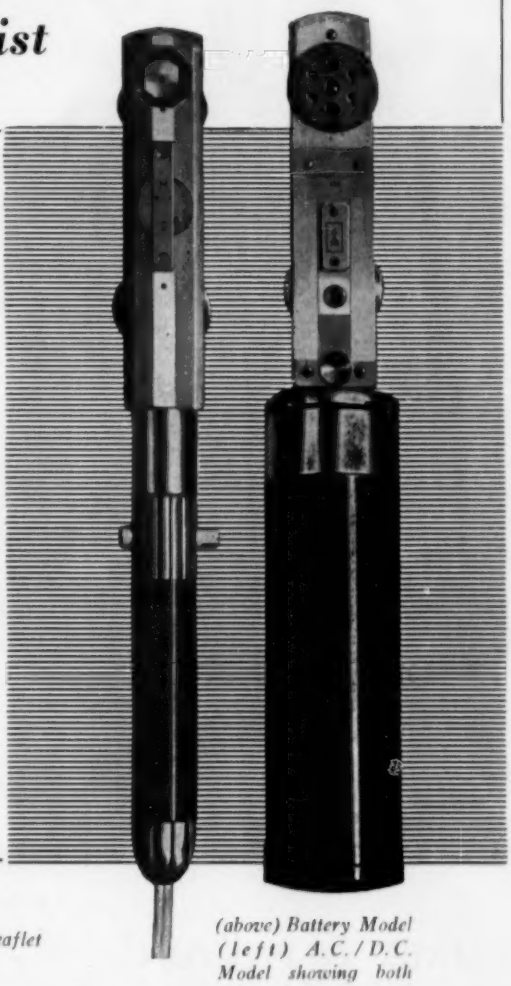

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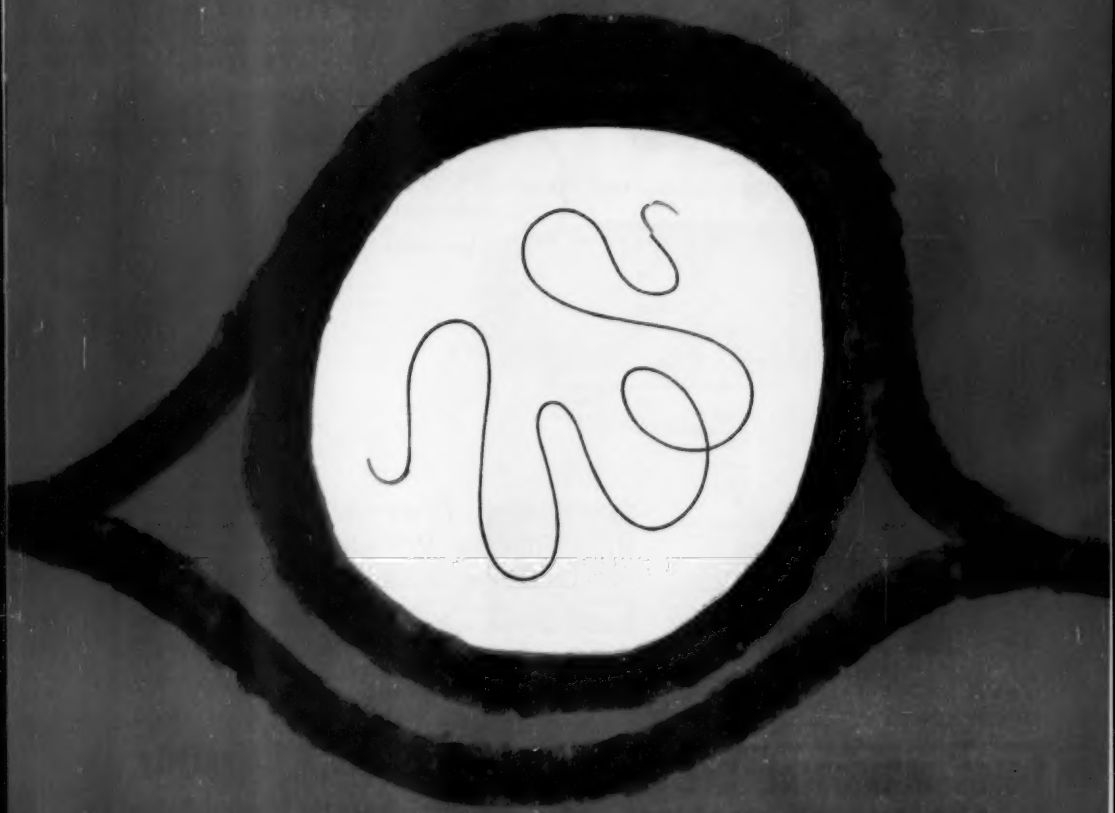

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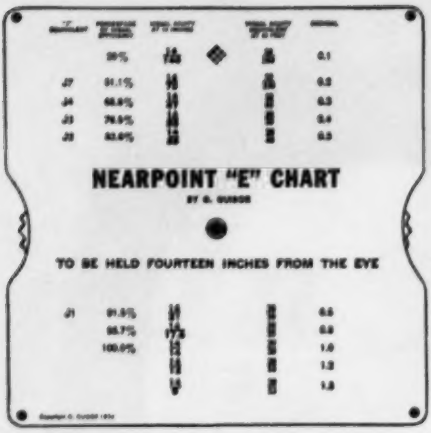

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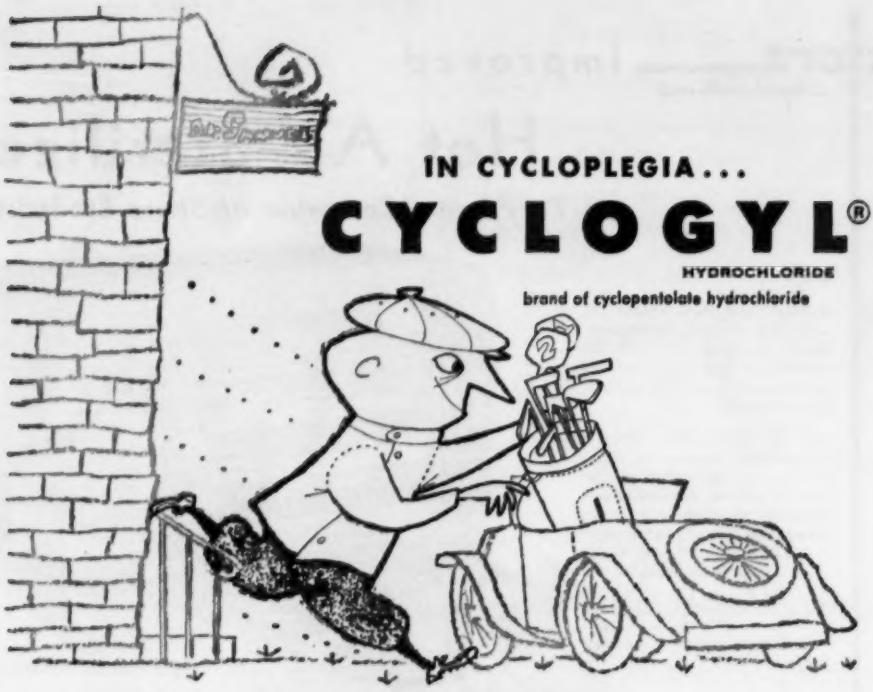

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New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Company, 1954, p. 189.

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Cyclogyl 0.5%	2	1.10	24†
Homatropine 2% or 4%	2	2.00	48

*Successive drops at five-minute intervals.

†Recovery time reduced to six hours after one-percent pilocarpine.

1. Gordon, D. M., and Ebrenberg, M. H.: Am. J. Ophth. 38:831 (Dec.) 1954.

"the chief handicap of maximum cycloplegia, namely its incapacitating effect, is minimized . . ."

Gettes, B. C.: A.M.A. Arch. Ophth. 51:467 (Apr.) 1954.

Cyclogyl, "by virtue of its brevity, rapidity of action, and consistent depth of cycloplegia, will be [a drug of choice] for routine refraction . . ."

Ehrlich, L. H.: New York J. Med. 53:3015 (Dec. 15) 1953.

Dosage:

Cycloplegia – One drop 1.0%, in each eye (or two drops of 0.5%) produces maximal cycloplegia in 30-60 minutes. Recovery time is normally 4-12 hours spontaneously. Pilocarpine reduces recovery time. In deeply pigmented eyes, 2 drops of 1.0% in each eye, instilled 10 minutes apart, achieves satisfactory cycloplegia in 98% of cases.

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Tonography in the Clinical Managment of Glaucoma

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I. Introduction

This paper presents conclusions based on 600 tonographic studies on 239 eyes with various types of glaucoma, with use of the method described by Grant.[1] We have repeated much of Grant's work * in glaucomatous eyes and have confirmed his data. In addition, we have directed particular effort toward determining the usefulness of tonography in the clinical management of glaucoma. The reliability of tonography was compared with the water provocative test in the diagnosis of chronic simple glaucoma. Tonographic values, before and during water provocative tests, were analyzed for any evidence that they might contribute toward explaining the mechanism of the rise in tension. The effects of miotics on tonographic values were observed for possible explanations of the mechanism of action of miotic agents in the treatment of glaucoma. An attempt was made to assess the value of tonography in the choice between medical and surgical treatment. Tonographic studies were also done on a group of patients which we have termed "glaucoma suspects," with ocular tensions in the upper limits of normal but showing little or no other evidence of glaucoma, and the results were compared to those of other diagnostic tests and clinical findings. Tonography was also done on miscellaneous types of glaucoma, and the results are reported.

II. Historical Review

Attempts at tonography were made in the past by Schiøtz,[4] Böck, Kronfeld, and Stough,[5] and others,† all of whom observed that the ocular tension fell more slowly in glaucomatous than in normal eyes under the influence of the pressure of tonometer applied repeatedly at short intervals or after prolonged application.

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* References 1-3 and 26.

† Smith,[6] cited by Böck[5]; Wegner, W.,[7] cited by Böck.[5]

Moses and Bruno [8] and, particularly, Grant,[1] working simultaneously, greatly refined the older tonographic methods. Moses and Bruno [8] reported a method of measuring the outflow of aqueous humor from the eye. They used either a certified Schiøtz or a Mueller electronic tonometer and applied the values which they obtained to Friedenwald's ‡ tonometric data and, from this, calculated aqueous outflow. They obtained a permanent record of the ocular tension during the study by simultaneously photographing the dial of the Mueller electronic tonometer.

Grant,[1] in 1950, reported his still more refined method for measuring the facility of outflow of aqueous humor and the net rate of aqueous flow. In 1951, he [3] reported extensive data as a result of studies upon normal and glaucomatous eyes. He used an electronic tonometer connected to a paper strip recorder to obtain a continuous tracing of the ocular tension, while the tonometer was continuously applied to the eye over a four- to five-minute period. Using values taken from the tracing, he was able to calculate the coefficient of facility of outflow of aqueous humor in terms of cubic millimeters per minute per millimeter of mercury pressure. For the details involved in the calculations, the reader is referred to Grant's [1] original article. Moses and Bruno,[8] in their method, expressed the rate of outflow of aqueous from the eye as cubic millimeters per minute at the average pressure in the eye during this procedure. Grant [1] expressed his results as a coefficient of the facility of aqueous outflow in terms of cubic millimeters per minute per millimeter of mercury pressure acting on the eye during the procedure. Friedenwald's § determination of the volume of corneal indentation and the intraocular pressure that corresponds to different scale readings and plunger loads during tonometry was essential to the development of tonography.

Stimulated by the work of Grant, we began to work with tonography and, in a previous paper,[12] reported a rather large number of tonographic studies on normal eyes which contributed to data already in the literature. These studies also served as a basis of control for our own technique by offering a comparison of our results with those of others, particularly Grant, whose data we largely confirmed. We found a range of coefficient of outflow of aqueous in normal eyes from 0.11 to 0.42 cu. mm/min/mm. Hg pressure. The average coefficient of outflow in 240 tracings on 140 normal eyes was 0.22 cu.mm/min/mm. Hg pressure, which was identical to that found by Grant. In evaluating repeated tracings on a large number of eyes, we found the method to be accurate to approximately ±0.04 cu.mm/min/mm. Hg pressure. We feel that this range of error, therefore, must be assumed for any individual tracing, at least from findings in our hands. In 94% of 140 normal eyes the coefficient of outflow was 0.16 cu.mm/min/mm. Hg pressure or more. Any value below 0.16 should, therefore, be regarded as suspicious of glaucoma, although a variation of ±0.04 must be assumed. No coefficient of outflow in our normal eyes was below 0.11, which is in agreement with the findings of Grant.

III. Tonography and the Gonioscopic Classification of Glaucoma

A. Classification of Primary Glaucoma

Grant's classic work in tonography has given almost incontrovertible evidence in support of the gonioscopic classification of glaucoma, first suggested by

‡ References 9-11.

§ References 9-11.

Barkan [13] and now widely accepted with only slight modification. This classification divides primary glaucoma into two main groups, based on width of the angle of the anterior chamber. Each type runs a characteristic clinical course and shows a different response to treatment. One has an open angle and has been referred to either as wide-angle or chronic simple glaucoma. This type of disease runs a chronic simple course. The other type is associated with a narrow angle and is referred to as narrow-angle glaucoma. It is characterized by acute congestive attacks. Narrow-angle glaucoma corresponds to an acute congestive glaucoma of the neurovascular classification, and wide-angle glaucoma corresponds to the chronic simple type. The systems of classification, therefore, run a parallel clinical course. The chief differences are in terminology, which is inconsequential, and in viewpoint regarding the mechanism of the disease, which is obviously basic. The gonioscopic classification of glaucoma assumes that the underlying disturbances in physiopathology are largely unknown, thus leaving the subject open to any consideration. Adherents of this classification insist only that there is a definite correlation between angle depth and type of glaucoma. The neurovascular school, on the other hand, is more restrictive, for it arbitrarily assumes a neurovascular origin for all primary glaucoma.

1. *Narrow-Angle Glaucoma.*—Acute congestive glaucoma invariably occurs in eyes with narrow angles (Fig. 1). We have never seen an acute attack of primary

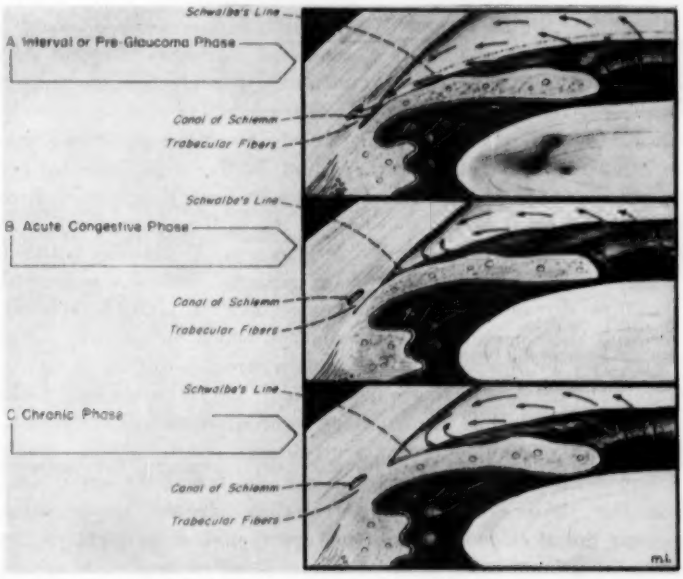

Fig. 1.—Drawings to illustrate various phases of narrow-angle glaucoma. *A*, interval, or preglaucoma, phase, illustrating very narrow but open angle with normal outflow of aqueous. *B*, acute congestive phase, root of iris in contact with trabecular fibers, preventing outflow of aqueous. *C*, chronic phase, permanent organic adhesion of root of iris to trabecular fibers as a result of protracted acute attack or repeated mild or subacute attacks.

glaucoma occurring in an eye where the angle was not closed during an acute attack, or very narrow during the interval between attacks. Narrowness of the angle, therefore, is assumed to be the basic, or underlying, cause. The tension becomes elevated only when the iris comes into contact with the trabecular fibers,

preventing the outflow of aqueous through this filter-like structure into the canal of Schlemm. Since the underlying cause of acute congestive glaucoma is a narrow angle, closure of the angle by the iris root can be due to one or more secondary factors. Some seem purely mechanical, such as pupillary dilatation in a dark room or by mydriatics. Some are neurovascular, such as acute congestive glaucoma following emotional upsets. Physiological iris bombé may play a part. These factors probably are all present in eyes having wide angles, but since angle closure ordinarily cannot take place in eyes with wide open angles, acute congestive glaucoma does not result. Narrow-angle glaucoma can readily be divided into three phases.

(*a*) Interval and Preglaucoma Phases: The ocular tension is normal during both the interval and preglaucoma phases of narrow-angle glaucoma. The interval phase can be said to exist in an eye which has had a previous known acute congestive attack that terminated either spontaneously or as a result of medical therapy. Preglaucoma is a term used by Gradle [14] to designate those eyes with very narrow angles, where the ocular tension could be made to rise with pupillary dilatation. In each type, because the tension is normal at the time of examination, the angle is assumed to be open functionally and aqueous outflow is assumed to be normal (Fig. 1*A*). The only abnormality is thought to be the close proximity of the iris to the corneoscleral wall of the angle, which subjects the eye to the danger of acute congestive attacks of glaucoma from angle closure (Fig. 1*A* and *B*). In 23 eyes with congestive narrow-angle glaucoma without medication and between attacks, de Roetth and Knighton [15] found an average coefficient of outflow of 0.20 cu.mm/min/mm. Hg pressure and an average net rate of flow of 3.18 cu.mm/min.

(*b*) Acute Congestive Phase: During attacks of acute congestive glaucoma, the iris is in contact with the trabecular portion of the angle, thereby preventing aqueous outflow (Fig. 1*B*). Grant,[3] de Roetth and Knighton,[15] Becker and Friedenwald,[16] and de Roetth [17] showed that the facility of aqueous outflow was markedly reduced during acute congestive glaucoma. Grant also noted that during the interval, or preglaucomatous phase, aqueous outflow was normal, which offered excellent support for these concepts. In 1951 Grant [3] reported studies on 10 eyes with acute narrow-angle glaucoma in which the pressure ranged from 49 to 79 mm. Hg and the coefficient of outflow, from 0 to 0.06 cu.mm/min/mm. Hg pressure. The net rate of flow ranged from 0.5 to 2.9 cu.mm/min. Goldmann,[18] using his fluorescein method for studying aqueous outflow, also found marked depression of aqueous outflow during acute attacks.

(*c*) Chronic Phase: In the chronic phase, the ocular tension is consistently elevated because the iris has become organically adherent to the corneoscleral wall. In many instances congestion of the eye is present (Fig. 1*C*). This phase can result from a fulminating acute attack or as an outgrowth of repeated mild acute attacks, called by Chandler [19] subacute glaucoma. Progressive anterior peripheral synechias form with recurring subacute rises in tension which cause increasing impairment in aqueous outflow and progressive rise in tension.

2. *Chronic Simple (Wide-Angle) Glaucoma.*—Gonioscopic concepts in chronic simple glaucoma have been especially vulnerable to criticism because of terminology. Repeated observations have shown that angle depth in this type of disease may, in different eyes, vary from wide open to very narrow (Fig. 2). The term "wide angle" is misleading. "Open angle" is preferable, because it is inferred

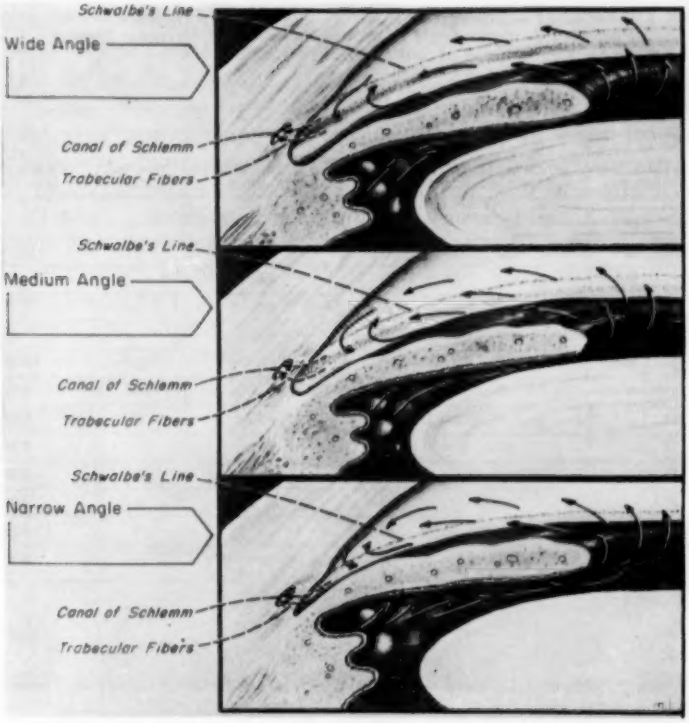

Fig. 2.—Drawings to illustrate occurrence of chronic simple (wide angle) glaucoma in angles of any width so long as aqueous has access to the trabecular fibers.

only that the angle is open, regardless of depth, and that the aqueous humor of the anterior chamber has free access to the trabecular region and the canal of Schlemm mechanism. The fact that the ocular tension is elevated constantly, even though the angle is open, suggests that this type of glaucoma is probably on the basis of increased production of aqueous or interference with its outflow. Tonographic studies offer strong evidence that this type of glaucoma is due to obstruction. The exact location of the obstruction remains obscure, but it probably lies in the trabecula, the canal of Schlemm, or the emissary vessels.

B. Presentation of Tonographic Observations in Various Types of Primary Glaucoma

All of the tonographic studies reported in this paper were done by us. The type of apparatus described by Grant [1] was employed. All values were calculated from tracings made on a Sanborn recorder. All eyes were studied gonioscopically by one of us (H.G.S.), and the disease was classified.

1. *Narrow-Angle Glaucoma.*—All of the eyes in this category had angles which were closed or extremely narrow, gonioscopically. This group, as a whole, serves to illustrate the different phases of narrow-angle glaucoma (Tables 1 and 2), and in general our tonographic observations support those of other authors. Except for the eyes with chronic narrow-angle glaucoma, all eyes were seen at least once during an acute phase with a sudden rise in tension. In six instances the acute phase was induced by provocative mydriasis tests, while in seven an

TABLE 1.—*Normal Facility of Outflow of Aqueous in Preglaucoma and Interval Phases of Narrow-Angle Glaucoma and Marked Decrease During Acute Congestive Phase*

Eye	Preglaucoma		Acute		Interval	
	T (Mm. Hg, Schiøtz)	C (CuMm./Min./ Mm. Press.)	T (Mm. Hg, Schiøtz)	C (CuMm./Min./ Mm. Press.)	I (Mm. Hg, Schiøtz)	C (CuMm./Min./ Mm. Press.)
1	18	0.22	55	0.00		
2	16	0.25	62+			
3	16	0.17	62+	0.01		
4	20	0.18	62+	0.05		
5	17	0.23	62+	0.02		
6	26	0.30	62+		20	0.23
7			72	0.01	10	0.18
8			50	0.05	30	0.12
9			63	0.02	17	0.25
10			77	0.02	15	0.23
11			62+		14	0.31
12			62+		16	0.28
13			40		21	0.15

TABLE 2.—*Marked Diminution in Facility of Outflow of Aqueous in Chronic Narrow-Angle Glaucoma*

Eye	Tonography Without Therapy		Tonography on Med. Therapy		Mechanism	
	T	C	T	C	Fulminating Acute Attack	Repeated Mild Acute Attacks
1	50	0.10	25	0.15	×	
2	53	0.03	50	0.01		×
3	60	0.06	28	0.03		×
4	5	0.06	33	0.10		×
5	83		35	0.08	×	
6	77	0.03			×	
7	54	0.05	25	0.12		×
8	41	0.09	22	0.15		×
9	46	0.07	22	0.10		×
10	40	0.08	16	0.01		×
11	83	0.00			×	
12	37	0.18				×
13	37	0.14				×
14	46	0.02				×
15	30	0.10				×
16	72	0.08			×	
17	77	0.05	..	....	×	
18	63	0.03	40	0.05	×	

Average C in 17 untreated eyes with chronic narrow-angle glaucoma=0.07 cu. mm./min./mm. press.
Average C in 10 medically treated eyes with chronic narrow-angle glaucoma=0.11 cu. mm./min./mm. press.

acute congestive attack of glaucoma was present when the patient was first seen.

(*a*) Interval and Preglaucoma Phases: (1) Preglaucoma. Tracings were done on six eyes during the phase of preglaucoma. Narrow angles were recognized as an incidental finding in all of these patients upon routine examination, and no previous symptoms of glaucoma could be elicited. The ocular tension in all of these eyes was within normal limits. The coefficient of outflow was normal prior to mydriasis tests and ranged from 0.17 to 0.32 cu.mm/min/mm. Hg pressure (Table 1). Acute attacks were then precipitated by pupillary dilatation, and tracings were done during the acute phase with high ocular tension in four eyes. These tracings, in contrast to those previously done, revealed a markedly diminished coefficient of outflow, which ranged from 0 to 0.05 cu.mm/min/mm. Hg pressure. This offered excellent support for the premise that the underlying cause of acute congestive glaucoma is a narrow angle and that the aqueous outflow is normal except during the acute attack, which occurs because of angle closure and consequent obstruction to aqueous outflow (Figs. 3A and 3B). Pre-

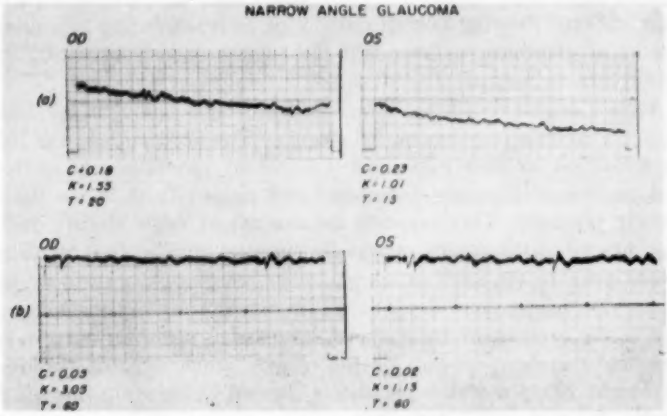

Fig. 3A.—Tonographic tracings illustrating outflow of aqueous in narrow-angle glaucoma. (*a*) Normal outflow during preglaucoma phase. (*b*) Marked diminution in outflow during acute congestive phase.

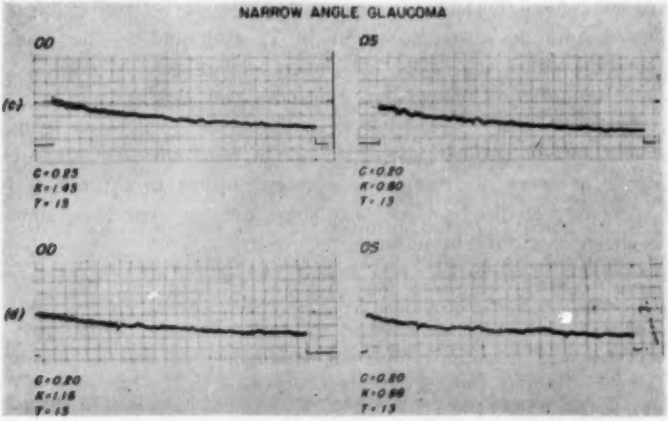

Fig. 3B.—(*c*) Normal outflow after reopening of angle by peripheral iridectomy. (*d*) Normal outflow during mydriasis test after peripheral iridectomy.

glaucoma seems to be an excellent term and is very descriptive of the type of eye which is predisposed to an attack of acute congestive glaucoma.

(2) Interval glaucoma. Eight eyes were seen during the phase of interval glaucoma when the tension was normal following a typical acute attack. One of these acute attacks had been induced by a mydriasis test. The acute attack had been terminated by medical treatment in six eyes and had resolved spontaneously in one eye. The facility of outflow was normal with one exception, eye No. 8, where it was questionably subnormal and associated with ocular tension readings which were constantly in the neighborhood of 30 mm. Hg (Schiøtz). These two findings seemed to indicate a partial residual obstruction of the angle as a result of permanent anterior peripheral synechias. The acute attack in eye No. 13 had occurred while the patient was viewing a movie but terminated spontaneously. Because of his symptoms, he had been referred to us for study. The ocular tension was normal when he was first seen, but he had extremely narrow angles and a positive darkroom mydriasis test. Aqueous outflow was recorded within normal limits after both the typical acute attack and the positive mydriasis test. These observations, showing normal outflow of aqueous during the interval after acute attacks of glaucoma, indicate that the angle reopens, permitting the ocular tension to return to normal.

(*b*) Acute Congestive Phase: Tracings were done on eight eyes during the phase of acute congestive glaucoma (Table 1). The acute attack was induced by pupillary dilatation in four eyes, and it occurred spontaneously in four. The facility of outflow was greatly diminished and ranged from 0.0 to 0.05 cu.mm/min/mm. Hg pressure. This supports the concept of angle closure during acute congestive attacks of the disease, especially since tracings in four of the eyes had been normal prior to the acute attack.

The net rate of aqueous flow, or K, in narrow-angle glaucoma is variable because it is the product of the original intraocular pressure and the coefficient of outflow and therefore depends on the relative impairment of outflow and the resultant height of intraocular pressure. Generally, the net rate of flow was lower during the acute congestive phase.

(*c*) Chronic Phase: Tonographic studies were done on 18 eyes with chronic congestive glaucoma due to permanent angle closure (Table 2). From the patient's symptomatology, the chronic congestive phase was believed to have developed from repeated mild or subacute attacks in 11 eyes and as the result of one fulminating acute attack in 7 eyes. The average coefficient of outflow in 17 untreated eyes with chronic congestive glaucoma was 0.07 cu.mm/min/mm. Hg pressure. In 10 medically treated eyes with chronic congestive glaucoma the average coefficient of outflow was 0.11 cu.mm/min/mm. Hg pressure. These values indicate a severe obstruction to aqueous outflow in chronic narrow-angle glaucoma, probably on the basis of peripheral anterior synechias, since it could not be completely overcome by miotics.

2. *Tonographic Observations in Chronic Simple (Wide Angle) Glaucoma.*—Tonographic studies were done on 162 eyes with classic chronic simple (wide angle) glaucoma. All were untreated at the time of study. Forty-four eyes had received no previous therapy, while the remainder had had no miotics for 48 hours or longer. Similar studies have been reported in the literature (Table 3).‖

‖ References 1-3, 15-17, and 20-24. Grant, W. M., and Trotter, R. R.: Outflow of Intraocular Fluid: Clinical Aspects, CIOMS Symposium on Glaucoma, Montreal, Canada, 1954.

TABLE 3.—*Summary of Available Data on Tonography in Chronic Simple (Wide Angle) Glaucoma*

Ref. No.	Author	Year	Eyes, No.	Average C	Range C	Average K	Range K	Comment
				(Cu.Mm./Min./Mm. Press.)		(Cu.Mm./Min.)		
3	Grant	1951	75		0-0.11	1.5	0-3.5	All types of glaucoma
20	Kronfeld	1952	34	0.099	0.026-0.182			
15	de Roetth and Knighton	1952	48	0.101		2.29		
21	Weekers and Prijot	1952	66	Diminished				
16	Becker and Friedenwald	1953		Diminished	0.00-0.15			
22	Mansheim	1953	30	Diminished	0.00-0.20			
*	Grant	1954		0.082		1.69		
23	Horwich and Breinin	1954	39	Diminished	0.00-0.22			
17	de Roetth	1954	48	Diminished	0.03-0.18			No diurnal change in C
24	de Roetth and Carroll	1955	38	Diminished	0.02-0.19		0.70-4.50	Before and after retrobulbar injections of procaine

* Grant, W. M., and Trotter, R. R.: Outflow of Intraocular Fluid: Clinical Aspects, CIOMS Symposium on Glaucoma, Montreal, Canada, 1954.

Nearly all workers agree that there is a definite impairment in the facility of outflow of eyes with chronic simple (wide angle) glaucoma as compared with healthy eyes, and there is general agreement that the impairment is proportional to the severity of the disease, being most marked in eyes where the tension is consistently high (Table V). In many papers careful classification of the disease had not been made.

In this paper the following diagnostic criteria were used: The angles of all of the eyes were open to gonioscopic examination. One hundred nine had an ocular tension consistently greater than 35 mm. Hg Schiøtz. Tension in the remaining 53 eyes ranged between 30 and 35 mm. Hg Schiøtz. Of these 53 eyes, the water provocative test caused a rise of 10 mm. Hg Schiøtz or more in 38 eyes and a rise of 6 to 10 mm. Hg Schiøtz in 14 eyes. The tension in the remaining eye was in the low 30's, and the water provocative test caused a rise of only 5 mm. Hg Schiøtz, but characteristic cupping of the optic nerve and a Roenne nasal visual field defect were present. In the group of 53 eyes whose ocular tension ranged from 30 to 35 mm. Hg Schiøtz, 11 showed cupping of the optic nerve that was suspected of being glaucomatous and 8 had definite cupping with a visual field defect. These diagnostic requirements are discussed to emphasize the fact that this group of 162 eyes had undoubted chronic simple (wide angle) glaucoma.

The average coefficient of outflow in these eyes with untreated chronic simple (wide angle) glaucoma was 0.121 cu.mm/min/mm. Hg pressure (Fig. 4). The range was from 0 to 0.30, cu.mm/min/mm. Hg, which was somewhat wider than that found by other observers. The average coefficient of outflow was therefore significantly less than the average of 0.22 cu.mm/min/mm. Hg pressure found by

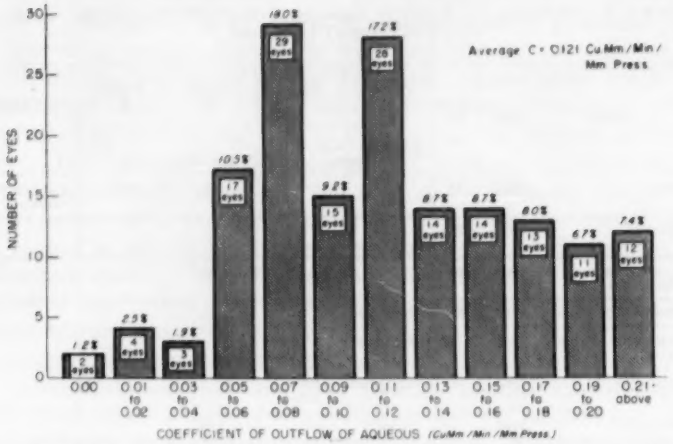

Fig. 4.—Distribution of the coefficient of outflow of aqueous in 162 eyes with untreated chronic simple (wide angle) glaucoma of varying degrees of severity.

Grant [3] in 118 normal eyes and by ourselves [12] in 140 normal eyes. The K value seems of no significance to the present discussion.

Chronic simple glaucoma shows a nearly constant impairment in aqueous outflow in contrast to the narrow-angle type, which has certain phases characterized by normal outflow of aqueous and others in which obstruction to outflow is complete or nearly complete. The presence of this constant impairment of aqueous outflow demonstrated by tonography and the fact that the trabecular region of the angle wall was visible upon gonioscopic examination in all of the eyes indicates that the impediment to aqueous outflow in chronic simple (wide angle) glaucoma is probably located in the corneoscleral wall at or beyond the trabecular fibers.

The impairment of aqueous outflow was found to be proportional to the level of ocular tension or severity of the disease (Fig. 5). This probably accounts for

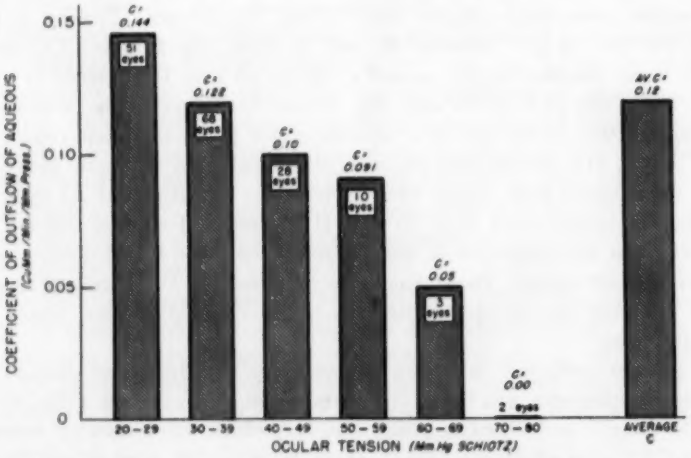

Fig. 5.—Graph correlating the coefficient of outflow of aqueous in 162 eyes having chronic simple (wide angle) glaucoma with ocular tension level at time of tracing.

the fact that the coefficient of outflow in 23% of the 162 eyes which we studied with chronic simple (wide angle) glaucoma showed a facility of outflow of 0.16 cu.mm/min/mm. Hg pressure or higher, because the disease was mild in many instances (Fig. 6). In our previous study of 140 normal eyes we found that tracings below 0.16 cu.mm/min./mm. Hg were unusual and should probably

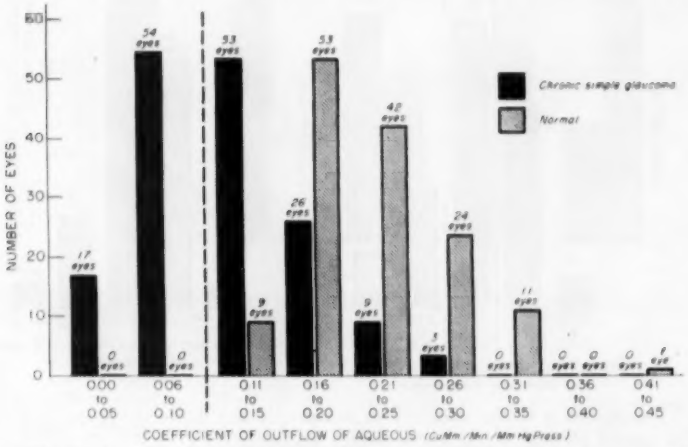

Fig. 6.—Distribution of coefficient of outflow of aqueous in 140 normal eyes and 162 eyes with chronic simple (wide angle) glaucoma.

be considered suggestive of glaucoma. However, in our hands, tracings, when repeated upon the same eye, showed an average error of ±0.04 cu.mm/min/mm. Hg pressure. This, of course, could throw any individual tracing of 0.19 cu.mm/min/mm. Hg or lower into an abnormal value, as would happen with 10% of the patients in this series of eyes with values of 0.16 to 0.19 cu.mm/min/mm. Hg pressure. Patients with very mild chronic simple glaucoma tend to have only a slightly diminished facility of outflow, just as their ocular tension may be consistently borderline from 24 to 35 mm. Hg Schiøtz. On the other hand, values which are only slightly diminished might, when the ±0.04 is added, be considered to be normal. The problem of a definitely abnormal coefficient of outflow in considering borderline values is even more troublesome than that involved in defining an arbitrary upper limit of ocular tension, because, in addition to uncertainty about the limits of tolerance of ocular tension of any one eye, there is a definite range of error which is more difficult to surmount. Several tension recordings can be repeated in a matter of a minute or two, while making more than one or two tonographic observations on the same eye involves serious obstacles.

IV. Tonography in the Diagnosis of Chronic Simple (Wide Angle) Glaucoma

A. Comparison of Tonography with the Water Provocative Test

Attempts were made to correlate the reliability of the water provocative test and tonography in the diagnosis of chronic simple glaucoma. The water provocative test is probably the most widely used provocative test for this type of disease. For purposes of comparison, water provocative tests and tonography were done on 105 eyes with known chronic simple glaucoma in which the diagnosis of the disease had been established by other clinical findings. The water provocative

test caused an increase in pressure of 6 mm. Hg Schiøtz or more in all but four eyes (Fig. 7). Since the group of patients which we have studied had other

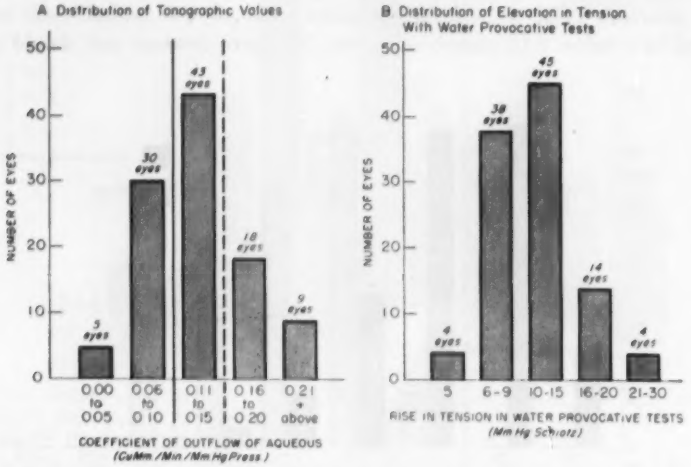

Fig. 7.—Comparison of the reliability of tonography and the water provocative test in 105 eyes with known chronic simple (wide angle) glaucoma.

classical signs of glaucoma by which diagnosis was established, it can be reasoned that rises in tension of 6 mm. Hg or more should be considered of significance, as has been suggested by Kronfeld.[20] Tonography revealed the facility of outflow to be 0.10 cu.mm/min/mm. Hg pressure or below in 35 eyes. Assuming that values of 0.10 cu.mm/min/mm. Hg pressure and below indicate definite glaucoma, we could conclude that tonography is less sensitive than the water provocative test, particularly if a rise of 6 mm. Hg or more is considered to be positive. One hundred one eyes showed such a rise. If 10 mm. Hg or more is required, the water provocative test remains more sensitive than tonography in our hands, because 63 of the eyes showed an elevation of this degree. If a coefficient of outflow of 0.15 cu.mm/min/mm. Hg pressure and below is considered significant, tonography was of greater value, since 78 eyes were included in this group. Values of 0.11 to 0.15 cu.mm/min/mm. Hg pressure are found in normal eyes and are therefore only suggestive.

In general, the facility of aqueous outflow was lower in eyes with higher tension and severer signs of glaucoma (Fig. 5). The values tended to be only slightly diminished on even normal eyes, where it is extremely difficult, in borderline cases, to make an arbitrary diagnosis on tonographic evidence. Our studies have also shown that the coefficient of aqueous outflow tends to be lower when the water provocative test causes a marked rise in tension and higher when there is little rise (Fig. 8). The water provocative test is easier to do and in our series of patients seemed more reliable than tonography in the diagnosis of chronic simple glaucoma, but, like any test, it must be evaluated against the entire clinical picture and should be used to supplement the over-all picture. Although the water provocative test is not infallible, it is simpler to do than tonography and gives fewer positive tests in supposedly nonglaucomatous eyes.

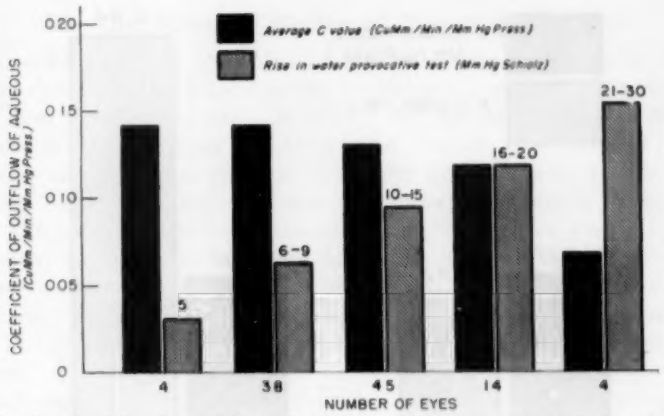

Fig. 8.—Relationship of coefficient of outflow of aqueous to increase in ocular tension during water provocative test in 105 eyes.

B. Effect of Water Provocative Test on Tonographic Values

De Roetth [25] studied the effect of water ingestion on 25 normal eyes and found that the ocular tension rose from only 1.0 to 4.0 mm. Hg Schiøtz. There was an associated increase in total rate of flow of aqueous and also in the facility of aqueous outflow found by tonography. He [17] also studied 22 eyes with chronic simple glaucoma. All of these patients had a positive water drinking test. In these, the facility of outflow changed very little. The rate of aqueous formation did show changes corresponding to the elevated tension. It increased as the ocular tension rose and returned to the pretest level as the tension fell. He believed, as did other workers, that the intake of water lowers the osmotic pressure of blood, thereby increasing the difference in osmotic pressure of the blood in aqueous humor. In turn, more water is pulled from the blood into the aqueous, increasing temporarily the rate of flow of aqueous humor into the anterior chamber. Becker and Friedenwald [16] studied the effects of water provocative tests for glaucoma on tonography and in 28 eyes found a decreased facility of outflow.

We did tonographic studies on 25 eyes before the ingestion of water and 45 minutes later, during the water provocative test, when the tension is usually most elevated (Fig. 9). The clinical diagnosis of chronic simple glaucoma had been fully established in 15 eyes, but in 10 of these the ocular tension had been only occasionally as high as the upper limits of normal and as a result they could be considered as "glaucoma suspects." The average coefficient of aqueous outflow for the entire group of 25 eyes did not change, nor did it change for either group when considered separately. The average K value increased from an average of 1.62 cu.mm. prior to the water provocative test to 2.84 cu.mm/min. when done during the test. We believe that this change in K value is significant and that our findings support those of de Roetth.

V. Tonographic Studies on Patients Suspected of Having Chronic Simple (Wide Angle) Glaucoma

Tonography was done on 58 eyes that we considered to be "glaucoma suspects." They showed no signs of glaucoma except an occasional tension reading at the upper limits of normal. In 40 eyes it was as high as 30 to 32 mm. Hg Schiøtz.

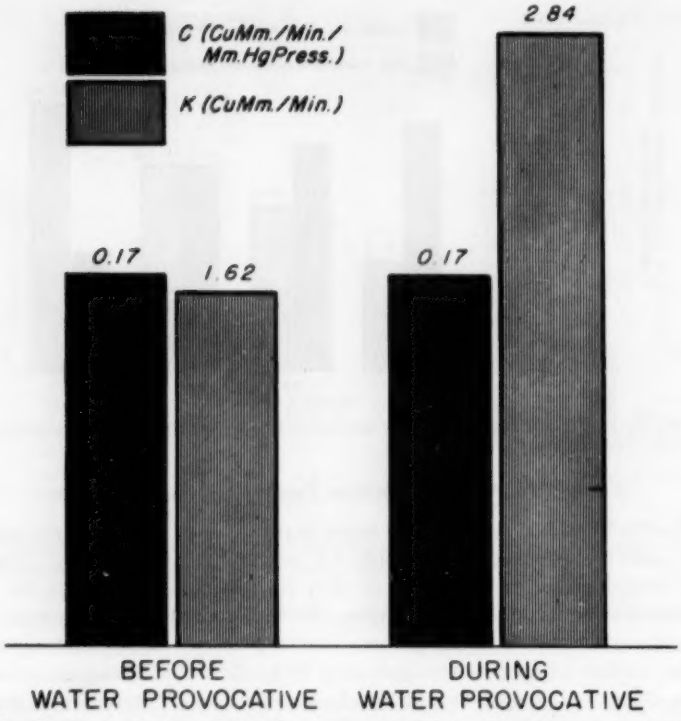

Fig. 9.—Graph showing no change in average coefficient of outflow of aqueous and rise in average net rate of flow during water provocative tests on 25 eyes—15 with chronic simple glaucoma and 10 with suspected glaucoma.

The usual clinical studies, including water provocative tests, had been done on these eyes beforehand. The angles of all eyes were open by gonioscopic examination. Some of the eyes had been followed for several years with no signs of glaucoma other than a borderline tension ever being noted. Suspicious optic nerves were found in nine and glaucoma in the fellow eye in five, and four were referred with the diagnosis of chronic simple glaucoma. Visual fields were normal in all eyes. The water provocative test showed a rise of 6 mm. Hg or more in 10 eyes. No eyes showed a coefficient of outflow of less than 0.11 cu.mm/min/mm. Hg pressure, a level which arbitrarily indicates glaucoma. The average C value was 0.19 cu.mm/min/mm. Hg pressure, and it ranged from 0.11 to 0.35 cu.mm/min/mm. Hg pressure. The coefficient of outflow was from 0.11 to 0.16 cu.mm/min/mm. Hg pressure in 16 eyes. That is a borderline range of values suggestive of glaucoma but one also found in normal eyes. Only three of these eyes had shown a positive water provocative test. If a tonographic value of 0.16 cu.mm/min/mm. Hg pressure or less is assumed to be definitely abnormal, which we feel is not justified, tonography is more sensitive than the water provocative test. If, however, values for the coefficient of outflow of only 0.10 or less can be considered arbitrarily low, tonography is less sensitive evidence.

VI. The Effect of Miotics on Tonographic Values

Ophthalmologists have speculated for years as to the mechanism of action of miotics in chronic simple glaucoma, but an adequate explanation has never been given. Grant [3] studied the effect of miotics and the rate of aqueous formation on glaucomatous eyes, using his tonographic method. He found a value of 1.34 cu.mm/min in 67 glaucomatous eyes under treatment with miotics, as compared with 1.45 cu.mm/min. in 85 eyes with untreated glaucoma. In a study of 15 eyes with primary glaucoma he found that the lowering of tension by miotics could usually be adequately accounted for by the degree of improvement of the coefficient of aqueous outflow. In 19 of 31 eyes, even though normal tensions were obtained, the facility of outflow commonly persisted somewhat below normal. He felt that this could be explained on the basis of a subnormal rate of aqueous formation.

Grant [3] stated that the lowering of tension in glaucoma by miotics is commonly found to be due to an improvement in facility of aqueous outflow. In narrow-angle glaucoma this results from opening of the angle, but in wide-angle glaucoma no significant change in appearance was observed, despite improvement in outflow. He found, as did we, that relief of an acute attack of glaucoma by miotics returns facility of outflow, tension, and rate of formation to normal. We also both found that in chronic narrow-angle glaucoma, where the presence of peripheral anterior synechias can be assumed, the facility of aqueous outflow improved but did not return to normal as did the tension. He suggested, therefore, that there might be a persistence of a somewhat subnormal rate of aqueous formation, as he had observed previously. He generalized by stating that the lowering of intraocular pressure by suppression of aqueous formation is a relatively uncommon mode of action for miotics but that instead miotics may act by increasing facility of aqueous outflow. Becker and Friedenwald [16] also found that miotics usually improved the facility of aqueous outflow in eyes with open-angle glaucoma and that this improvement was associated with a decreased ocular tension. De Roetth

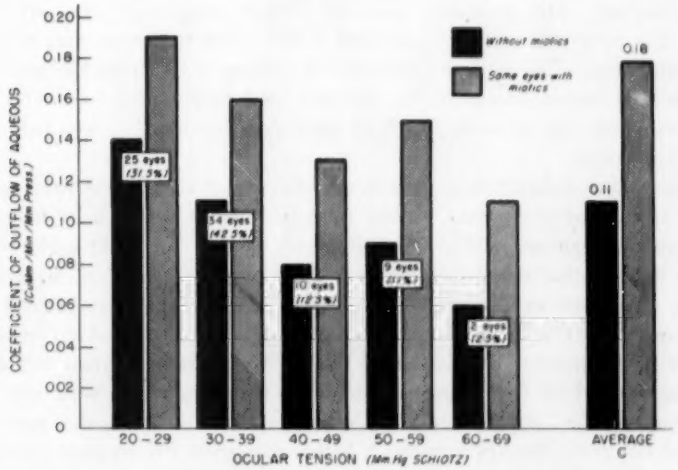

Fig. 10.—The effect of miotic therapy on the coefficient of outflow of aqueous in 80 eyes with chronic simple (wide angle) glaucoma, arranged in groups according to levels of ocular tension while untreated.

and Knighton [15] also found that miotics increased the facility of aqueous outflow in the majority of eyes and, although it returned to normal in only 60%, the tension was controlled in 80%.

We studied 80 untreated eyes with chronic simple glaucoma, either prior to treatment or 48 hours or more after the patients had discontinued all miotic therapy. The average coefficient of outflow was 0.11 cu.mm/min/mm. Hg (Fig. 10). The average coefficient of outflow in this same group of eyes, on miotic therapy, was 0.18 cu.mm/min/mm. Hg. There was no particular relation to ocular tension. The K value was unchanged. Although the increase in outflow of aqueous was never as dramatic as the increase which occurred following the termination of an acute attack of glaucoma by miotic therapy, we believe these findings are significant and indicate that the action of miotics is through the mechanism of increased aqueous outflow.

VII. Tonography in the Choice of a Medical or Surgical Regimen in Chronic Simple Glaucoma

We have attempted to evaluate the effect of medical therapy in terms of progression of visual field loss in relationship to an impaired aqueous outflow. To do so, we considered only those eyes with chronic simple (wide angle) glaucoma which had been followed for a period of one year or longer. This group included 73 eyes treated with miotics for a period from 1 to 16 years, in which aqueous outflow studies were performed while the eyes were on miotic therapy (Table 4).

Sixty-one eyes (82%) had normal visual fields when first seen and suffered no further loss of field on miotic therapy over a period of from 1 to 16 years. The average coefficient of aqueous outflow in this group was 0.16 cu.mm/min/mm. Hg pressure. The range was from 0.05 to 0.31 cu.mm. Six eyes (9%) had a visual field defect when first seen and were treated medically for 1 to 16 years, or an average period of 8 years, during which time no further loss of field occurred. The average coefficient of outflow in these eyes with treatment was 0.16 cu.mm/min/mm. Hg pressure, and the values ranged from 0.10 to 0.30 cu.mm. Six eyes (9%) with visual field defect when first seen were treated for one to two years. The average coefficient of outflow with miotic therapy in these eyes was 0.05 cu.mm/min/mm. Hg pressure, and they varied from 0.00 to 0.13 cu.mm/min/mm. Hg pressure. Each of these eyes continued to lose field in spite of miotic therapy.

These studies indicate that, in general, eyes which lose visual field on miotic therapy have a lower aqueous outflow than eyes which retain their field. However, impaired aqueous outflow during miotic therapy for wide-angle glaucoma does not indicate that visual field loss will occur or serve as an indication for surgery for any given eye, because of the wide range of figures obtained by us. Sixty-seven eyes (92%) with chronic simple glaucoma showed no visual field defect or no progression of visual field loss on miotic therapy when followed for an average period of five years, and some of them showed a very low facility of aqueous outflow. Progressive loss of visual field or an ocular tension uncontrolled on miotic therapy remains a better indication for surgical intervention in chronic simple glaucoma than a failure of miotics to bring about a normal coefficient of aqueous outflow.

TABLE 4.—*Relationship of Visual Fields to Coefficient of Outflow of Aqueous in Seventy-Three Eyes with Chronic Simple (Wide Angle) Glaucoma Treated with Miotics for One Year or Longer*

Period of Treatment, Yr.	Normal Visual Field			Visual Field Defect Without Progression			Visual Field Defect With Progression		
	Eyes, No.	Average C (Cu.Mm./Min./Mm. Hg Press.)	Range of C (Cu.Mm./Min./Mm. Hg Press.)	Eyes, No.	Average C (Cu.Mm./Min./Mm. Hg Press.)	Range of C (Cu.Mm./Min./Mm. Hg Press.)	Eyes, No.	Average C (Cu.Mm./Min./Mm. Hg Press.)	Range of C (Cu.Mm./Min./Mm. Hg Press.)
1-2	22	0.14	0.05-0.25	2	0.12	0.10-0.13	6	0.05	0.00-0.13
3-4	21	0.16	0.07-0.27						
5-6	6	0.17	0.13-0.25	1	0.30	0.30			
7-8	5	0.19	0.13-0.26						
9-10	6	0.21	0.14-0.31						
11-16	1	0.18	0.18	3	0.16	0.13-0.18			
Total	61			6			6		
Av., 5 yr.		0.16			0.16			0.05	

VIII. Aphakic Glaucoma

Tracings were done on 16 eyes with a diagnosis of aphakic glaucoma while they were still untreated and on 15 eyes with aphakic glaucoma during miotic therapy (Table 5). In 16 eyes with untreated aphakic glaucoma, the average

TABLE 5.—*Average Coefficient of Outflow of Aqueous in 239 Eyes with Untreated Glaucoma of All Types*

	Number of Eyes	Average C	Average K
Chronic simple glaucoma	162	0.12	2.33
Narrow-angle glaucoma			
Acute phase	8	0.02	1.59
Chronic phase	18	0.07	2.41
Secondary glaucoma			
Aphakic glaucoma	16	0.09	1.84
Uveitis, glaucoma capsulare, etc.	19	0.09	2.14
Juvenile glaucoma	16	0.08	1.88
Total number of eyes =	239		
Average C (cu.mm./min./mm./press.) =		0.111	
Average K (cu.mm./min.) =			2.24

coefficient of outflow was 0.09 cu.mm/min/mm. Hg pressure and the range was from 0.02 to 0.26 cu.mm/min/mm. Hg pressure. The average net rate of flow in these eyes was 1.84 cu.mm/min. Tonographic studies on 15 eyes treated with isoflurophate (DFP) showed an average coefficient of outflow of 0.17 cu.mm/min/mm. Hg pressure. Here the range was from 0.03 to 0.30 cu.mm/min/mm. Hg pressure. The average net rate of flow in the treated eyes was 1.95 cu.mm/min. Grant [3] reported an average coefficient of outflow of 0.19 cu.mm. in 10 aphakic eyes, and de Roetth and Knighton [15] found that 9 of 10 eyes with aphakic glaucoma showed a lower than normal rate of aqueous outflow in spite of miotics; 7 of these eyes had normal tensions with miotics.

IX. Secondary Glaucoma

Tonographic studies on 19 eyes with untreated secondary glaucoma, which was due to uveitis in 16, revealed an average coefficient of outflow of 0.09 cu.mm/min/mm. Hg pressure. The average net rate of flow was 2.14 cu.mm/min. (Table 5). Grant studied 18 eyes with secondary glaucoma and found that the elevation in tension was associated with diminished facility of aqueous outflow. Becker and Friedenwald [16] reported similar findings. De Roetth and Knighton [15] reported two cases of secondary glaucoma and found that the coefficient of outflow was normal without miotics in one eye and in the other eye the coefficient of outflow improved after miotics.

X. Primary Juvenile Glaucoma

In studying 16 eyes with the diagnosis of primary juvenile glaucoma, ages from 10 to 32 years, an average coefficient of outflow of 0.08 cu.mm/min/mm.

Hg pressure and an average net rate of flow of 1.88 cu.mm/min. were found (Table 5).

Comment

This paper presents the results of tonographic studies on 236 eyes with glaucoma of various types. Particular effort is made to help assess the value of tonography in the practical management of glaucoma. Grant has contributed an invaluable method for fundamental research in certain phases of glaucoma, particularly regarding the flow of aqueous into and from the globe. His studies, which are supported by most other observers, including ourselves, strongly support the gonioscopic classification and concepts of primary glaucoma. They indicate that the underlying cause of acute congestive glaucoma is a narrow angle. Except for narrowness of the angle, the eye is normal and behaves in a normal manner. The flow of aqueous from the eye is normal during periods of normal tension. Acute congestive attacks result from closure of the angle by the root of the iris, a concept supported by the finding of a marked diminution of aqueous outflow by tonography. In narrow-angle glaucoma, during phases of normal tension, either prior to a mydriasis test or following the termination of an acute attack, aqueous outflow is within normal limits, and it is markedly diminished during acute congestive attacks, when the angle is assumed to be closed. In chronic congestive glaucoma, after partial or complete angle closure has resulted from synechia formation, diminution in aqueous outflow is in proportion to the level of ocular tension or, in other words, to the extent of the synechia formation.

Tonography in chronic simple (wide angle) glaucoma indicates an obstruction somewhere in the corneoscleral wall, in the canal of Schlemm, or in the channels which carry aqueous away from the trabecular and canal of Schlemm mechanisms. The obstruction is usually in proportion to the severity of the glaucoma. When the disease is mild and the tension low, the aqueous outflow can be within normal tonographic limits, but when it is severe and the tension is high the impairment in outflow is usually definitely diminished.

An attempt was made to compare the reliability of the water provocative test and tonography in the diagnosis of chronic simple (wide angle) glaucoma. Our data seem to indicate that the water provocative test is more reliable than tonography, especially if significance is attached to rises in ocular tension of 6 mm. Hg or more. In comparing a series of patients suspected of having glaucoma and another group where the diagnosis was clinically obvious for reasons other than provocative tests, we are convinced that a diagnosis must be made on the over-all picture, no single one diagnostic feature being infallible. An ocular tension of over 35 mm. Hg seems indicative of chronic simple glaucoma if the angle is open. Cupping of the optic nerve and visual field defects are diagnostic, even with tension levels within the upper limits of normal. Careful observation usually demonstrates occasional higher tension readings in such eyes. Provocative tests can be very helpful in this type of eye. In our experience low-tension glaucoma, where cupping of the optic nerve and glaucomatous visual field changes occur in the presence of a consistently normal tension and negative provocative tests, is extremely rare. Great care must be taken to exclude causes other than glaucoma. If other findings are questionable, and the water provocative test is positive, a diagnosis of chronic simple glaucoma seems justified, because the water test rarely gives what might be called a false rise. Tonography in our patients seemed less reliable than the water provocative test, although any patient showing a coefficient

of aqueous outflow of 0.15 cu.mm/min/mm. Hg pressure or less should be held under suspicion. An aqueous outflow of 0.11 cu.mm/min/mm. Hg pressure or less is probably indicative of glaucoma, because neither we nor Grant have found a normal eye to give such values.

The effect of miotics on aqueous outflow was also studied. In 80 eyes we found the C value to increase from 0.11 cu.mm/min/mm. Hg pressure in untreated eyes to 0.18 cu.mm/min/mm. Hg pressure in eyes under miotic therapy. This change seems significant, since there was no change in the K value. We do not feel that tonography is sufficiently reliable to influence the choice of medical or surgical treatment in any given eye, although there is a definite correlation between progression of the disease and poor aqueous outflow. Decision must continue to be made on the basis of the over-all clinical picture. The two most reliable criteria are visual fields done on a tangent screen with a small test object and repeated recording of ocular tension.

Sixteen eyes with aphakic glaucoma were studied; the average coefficient of outflow was found to be 0.09 cu.mm/min/mm. Hg pressure. We believe this figure to be of significance and to indicate an obstructive origin of the disease. This was also true of juvenile glaucoma, where an average coefficient of outflow in 16 eyes was 0.08 cu.mm/min/mm. Hg pressure.

Tonography offers great promise as a tool for conducting fundamental investigations into glaucoma. It has already contributed much to our basic knowledge of the disease. It has lent brilliant support to the gonioscopic concepts of glaucoma and has given a much better picture of the behavior of aqueous outflow, in various types of glaucoma as well as in the normal eye. Tonography in our hands has not proved to be as reliable in the diagnosis of chronic simple (wide angle) glaucoma as the water provocative test. Although the coefficient of acqueous outflow is related to the severity of chronic (wide angle) glaucoma, it does not serve as a reliable indication that medical treatment has failed and surgical intervention is indicated. Our two best criteria for success or failure continue to be repeated careful visual field studies and recordings of ocular tension. It is of considerable value in helping to determine the extent of obstruction to aqueous outflow by peripheral anterior synechias in narrow-angle glaucoma, and we believe that it offers considerable help in the choice between peripheral iridectomy, which reopens the angle and reestablishes a normal outflow of aqueous in the absence of peripheral anterior synechias, and iridencleisis, which is a filtering operation and should be done in the presence of synechias which have interfered with aqueous outflow. This distinction, of course, can also be made by repeat recordings of tension with the eye under the effect of miotics. If the tension remains abnormally high, the presence of extensive peripheral anterior synechias can be assumed.

The greatest clinical value of tonography, at least in our own hands, rests in the evaluation of narrow-angle glaucoma and as an adjunct in the diagnosis of chronic simple glaucoma. In our experience it did not seem as reliable as the water provocative test, but observations by other workers on larger numbers of patients will be necessary. While tonography can be helpful in the management of glaucoma, it does not supplant good clinical judgment and established methods.

Summary

Tonography, as shown by Grant, offers valuable support to the gonioscopic classification of glaucoma. The coefficient of aqueous outflow is diminished in

chronic simple (wide angle) glaucoma usually in proportion to the severity of the disease.

Tonography indicates that acute congestive glaucoma occurs as a result of angle closure. Aqueous outflow is markedly diminished during acute congestive attacks and is normal after the attack is terminated by medical means.

Tonography does not seem to be as reliable a diagnostic test in chronic simple (wide angle) glaucoma as the water provocative test. Tonographic findings are the least conclusive in those eyes where the disease is mild and the diagnosis the most difficult. Tonographic values in this group of eyes is usually within the lower limits of values obtained in normal eyes.

Tonography suggests that the water provocative test causes a rise in intraocular tension by causing an increased rate of aqueous flow through the eye.

Miotics cause an increase in the coefficient of aqueous outflow.

The coefficient of aqueous outflow is probably not a reliable criterion of success or failure of medical treatment.

The coefficient of aqueous outflow is diminished in glaucoma after cataract extraction, glaucoma secondary to inflammatory process, and juvenile glaucoma.

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A Modification of the Friedenwald-Guyton Ptosis Operation

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All ptosis procedures may be classified into five groups: (1) simple resection of the skin and/or orbicularis, (2) operations utilizing the superior rectus muscle, (3) operations utilizing the frontalis muscle, (4) operations enhancing the effect of the levator muscle, and (5) procedures which artificially suspend the lid, as in suturing it to the orbital wall.

The first group is without permanent effect, and the fifth group is dangerous in that a lid suspended high enough to correct the ptosis will not protect the cornea and will not follow the eye on looking down.

If an infant has a normal muscle balance and a ptosis operation utilizing the superior rectus muscle is performed, a sufficient impairment of the muscle balance may occur that amblyopia will ensue. This type of procedure also carries with it the risk of corneal exposure. These two complications contraindicate superior rectus procedures in most instances.

The majority of surgeons agree that the levator-strengthening operations are usually the procedure of choice, but these operations can be difficult to perform and to evaluate in young infants. In this situation the simpler operation utilizing the frontalis muscle is indicated.

In 1948 Friedenwald and Guyton introduced a simple effective ptosis operation.[1] Their technique utilized the frontalis muscle by the means of a single rhomboid-shaped suture.

Technique of the Original Operation

The following brief description of the original Friedenwald-Guyton technique is quoted from their article. "Two small stab incisions are made at the upper border of the brow, one 5 mm. from its nasal termination and the other approximately 3 cm. lateral to the first. Each of these incisions goes down to periosteum. Two tiny incisions are made through the skin, 2 mm. above the upper lid margin and about 2 cm. apart, placed symmetrically so that they lie about 7 mm. from the nasal and lateral canthi, respectively. A braided white-silk suture (size from 2-0 to No. 2) on a No. 5 three-eights curve surgical cutting needle is inserted through the upper nasal of these four tiny incisions, through the fascial termination of the frontalis above the brow (just over the periosteum of the frontal bone), and out through the upper lateral incision. From here the suture is carried down through the lid along the under surface of the orbicularis to emerge through

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the lower lateral incision adjacent to the lid margin; then through the dermis, 2 mm. above the lid margin, to emerge through the lower nasal incision; then along the under surface of the orbicularis to emerge through the upper nasal incision. The suture is tied with the knot in the depths of the upper nasal incision. As the suture is tied, it is pulled tight enough to elevate the upper lid 2 mm. above the desired final position." (Fig. 1.)

Comment on the Original Operation

The operation met with immediate and wide acceptance because it is fast and easy to do and the results are good and can be evaluated immediately. In the original series of 31 operations, late infections occurred around the sutures in three cases. This late complication of infection of the suture tract has occurred with sufficient frequency that many surgeons have discarded the procedure.

It is probable that the late infections are caused by bacteria which gain access to the suture tract from the many modified sweat and oil glands which lie near the lid margin. Friedenwald and Guyton felt that it was necessary to place the inferior side of the rhomboidal suture very close to the lid margin in order to anchor it firmly in this tissue. This provided a firm anchorage but predisposed to late infection.

If the inferior side of the suture could be firmly anchored in the region of the normal lid fold, and not passed into the tarsus, the suture would not be placed close to lid glands and the risk of late infection would be removed. In this position, however, the suture would have to be secured by other sutures, in order that it would not be pulled away from the lid margin.

Modification of the Original Operation

The following modification of the Friedenwald-Guyton ptosis operation should preserve the advantages of a quick, simple, and easily evaluated operation while avoiding the one frequent and serious complication—late infection. The modification consists of placing the inferior side of the rhomboidal suture at the level of the normal lid fold and anchoring it there with other sutures.

The technique is as follows: *Step 1. The Incisions.*—Two small stab incisions are made at the upper border of the brow, one 5 mm. from the nasal termination, and the other approximately 3 cm. lateral to the first—exactly as was done in the original Friedenwald-Guyton procedure. Each of these incisions goes down to periosteum (Fig. 2 *A-D*).

Two similar incisions are made through the skin at the level of the normal lid fold, or where the lid fold should be. These must be placed closer together than the brow incisions (Fig. 2*B-C*).

Step 2. The Placing of the First Portion of the Main Suture.—A strong light-colored braided nonabsorbable surgical (silk or linen) suture on a No. 5 three-eighths curve surgical cutting needle is inserted through the upper nasal of these four tiny incisions (Fig. 3 *A*). The needle is inserted deep, just over the periosteum of the frontal bone, and carried inferiorly to emerge through the lower nasal incision (Fig. 3 *B*). The needle is reinserted into this same lower nasal incision, but superficially this time, and carried under the region of the normal skin fold until the point emerges through the lower temporal incision (Fig. 3 *C*).

Step 3. The Placing of the First Anchoring Suture.—While this large three-eighths curve needle is still in place with its shaft extending from incision *B* to

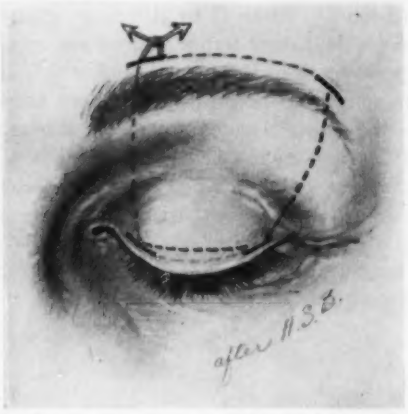

Fig. 1.—Diagram of original Friedenwald-Guyton suture.

Fig. 2.—Location of incisions.

incision *C* and its point emerging from the latter, a 0000 silk suture on a half curve needle is placed under the shaft of the large needle (Fig. 3 *E*). This 0000 silk suture is made to emerge 2 mm. above its point of entry into the skin, but it is not tied. The shaft of the three-eighths curve needle has served as a guide so that the 0000 silk suture has been inserted around the path of the larger suture. This anchors the larger suture and also helps to form a lid fold.

Step 4. The Placing of the Rest of the Main Suture.—The large needle with its main suture is now pulled out of incision *C* and reinserted. The main suture is not pulled entirely through, so that a loop of the main suture is allowed to remain protruding out of incision *B*. (Fig. 3 *F*). The large needle is made to emerge through incision *D*, but a loop of suture is allowed to remain protruding through incision *C*. The large needle is now carried from incision *D* to incision *A*.

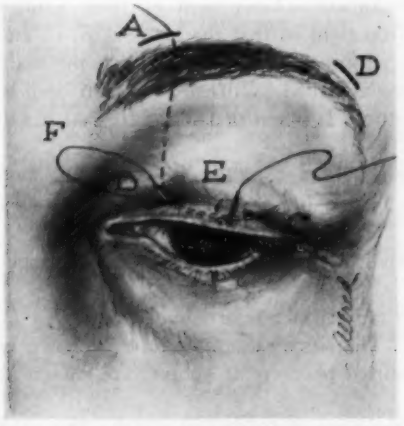

Fig. 3.—Placing of the first portion of the main suture and first anchoring suture.

Fig. 4.—Placing of the remainder of the main sutures.

Similarly, a loop of suture remains at incision *D*. From *D* to *A* it is necessary for the needle to be carried very deep through the fascial termination of the frontalis, just above the brow (just over the periosteum of the frontal bone).

At this stage of the operation the main suture has been placed and runs from *A* to *B* to *C* to *D* in Figure 4. A loop of the suture remains protruding through the incision at *B*, *C*, and *D*. A suture at *E* has been inserted but not tied.

Step 5. The Placing of Anchoring Sutures.—We are now ready to place anchoring sutures at *A*, *B*, *C*, and *D*. Incision *B* is held apart with retractors. A 0000 silk suture is placed through the loop of the main suture at *B*. This anchoring suture is placed deep in the tissue. This suture is shown as *F-F'* in Figure 5 and in the enlargement in Figure 5. Similar sutures are placed at *C*, *D*, and *A*.

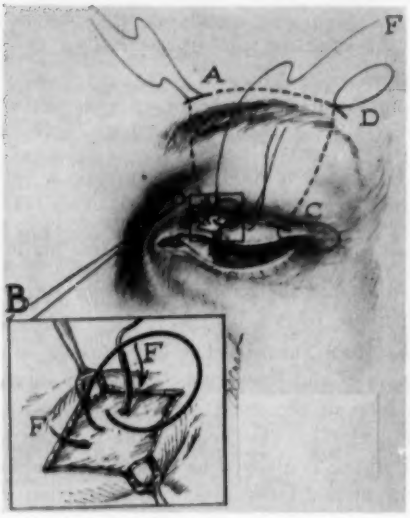

Fig. 5.—Placing of the anchoring sutures.

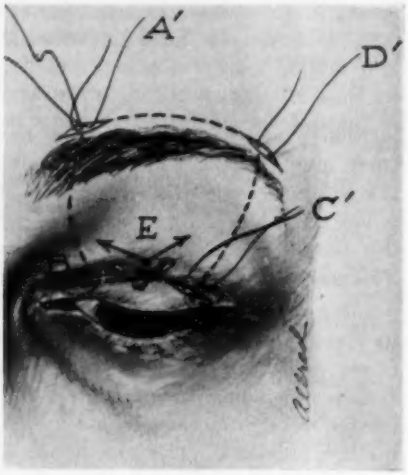

Fig. 6.—The anchoring of the main suture.

Step 6. The Anchoring of the Main Suture.—After each of these sutures has been placed, the main suture is pulled up tight so that the loops at *B*, *C*, and *D* no longer exist. The loop of the main suture at *C* is pulled so that the main suture is tight at *B*. As soon as this is accomplished, suture *F-F'* is tied deep in wound *B*, cut short, and left as a buried suture. It is not tied so tightly that it will easily cut through tissues.

The loop of the main suture at incision *D* is now pulled on so that the loop no longer exists at incision *C*. As soon as this is accomplished, the anchoring suture at incision *C* is tied and cut.

At this stage suture *E*, previously inserted, is tied over a short piece of rubber tubing (Fig. 6).

We now have the main suture drawn taut from *A* through *B* and *C* to *D*. We have it well anchored at *B*, *E*, and *C*. The situation at this time is shown in Figure 7, in which all buried sutures or buried portions of sutures are shown as dotted lines.

Step 7. The Tightening of the Main Suture and Raising the Lid.—The next step is to pull the main suture tight at *A*; each limb of the suture should have the

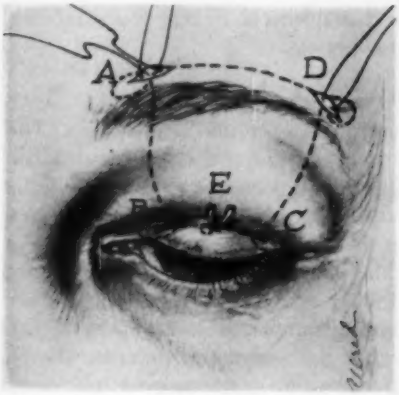

Fig. 7.—The tightening of the main suture.

Fig. 8.—Diagram of original Friedenwald-Guyton suture slipping.

proper tension in it so that the lid is lifted a millimeter or two above the limbus. The main suture is now securely tied at *A*, and cut off. The anchoring sutures at *A* and *D* are now tied and cut.

The operation is now complete, aside from closing the stab incisions with a subcuticular stitch. A Frost suture is placed in the lower lid to pull it up over the cornea. Any ophthalmic ointment is placed over the sutures to prevent the sutures from adhering to the patch. The patient is dismissed from the hospital whenever he has recovered from the anesthetic. Six days postoperatively the suture at *E* is removed.

Comment on the Modification of the Original Operation

I have not had a large series of cases of this modification of the Friedenwald-Guyton operation. This procedure has been done, with satisfaction and without difficulty. It is offered as a means of accomplishing the Friedenwald-Guyton technique with only slightly more difficulty and without great danger of late infection. It has the added advantage of securer anchoring of the suture, so that there is less tendency for it to cut through tissue and so diminish the effect. This last complication has been experienced by me and by others, and it is shown diagramatically in Figure 8, in which the suture (dotted line) has been pulled away from point *D*. It is felt that the present modification, with the securer anchoring of the corners of the main rhomboidal suture may diminish the chance of this complication.

This operation, like the original Friedenwald-Guyton one, is especially indicated in very young infants with a ptosis sufficiently marked that vision is obstructed. An operation is indicated in order to avoid amblyopia, but such procedures as Blascovic's operation or its modifications are difficult to perform and difficult to evaluate in these very young infants. The present procedure is excellent to temporarily raise the lid so that amblyopia can be avoided until a subsequent levator-shortening procedure can be performed after the tissues have developed. It does not result in a muscle imbalance, and amblyopia resulting from this imbalance, as those procedures which utilize the superior rectus muscle often do. It does not carry with it the hazard of late infection such as the original

Friedenwald-Guyton operation did, and yet it is simple to do in very young infants, unlike the operations which utilize the levator muscle.

Summary

A modification of the Friedenwald-Guyton ptosis operation is presented. The original operation was simple to perform and effective, but the incidence of late postoperative infection was very high. These infections occurred because the suture was placed close to the lid margin, and bacteria from the glands in this area readily gained access to the suture tract. In the modification presented the lower arm of the suture is placed at the level of the lid fold. At this level the suture cannot be anchored as securely; therefore, it is necessary to provide a firmer anchorage by the use of supplementary anchoring sutures. This modification may prevent late infections, decrease the likelihood of late slipping of the main suture, and yet not make the operation very much more time-consuming or difficult.

2400 Clay St. (15).

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Effect of Intravenous Typhoid Vaccine on Plasma Adrenal Cortical Steriods

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Despite the fact that intravenous typhoid vaccine has been used in the treatment of inflammatory diseases of the eye for over 30 years, its mode of action has remained obscure. Many theories have been advanced in an attempt to explain the dramatic benefit which clinicians have observed, in some cases, following typhoid vaccine treatment. However, the underlying mechanism of this treatment is still unknown.

In the past decade, as more information has accumulated concerning the physiology of the adrenal cortex, the assumption has grown among ophthalmologists that typhoid vaccine exerts its beneficial effects by activating the adrenal gland. It is postulated that the injection of typhoid vaccine provides a stressful stimulus and that the pituitary-adrenal axis responds with the release of endogenous adrenocorticosteroids. This assumption is supported by several experimental facts: Intravenous typhoid vaccine has been shown to cause depletion of cholesterol in the adrenal cortex of rats.[1] In human subjects, Arendhorst and Falls showed that typhoid vaccine therapy caused an eosinopenia which correlated roughly with the magnitude of the temperature rise.[2] More directly, Rosen [3] and Conn [4] independently demonstrated increases in urinary 17-ketosteroid and "corticoid" excretion in patients after typhoid vaccine therapy.

Recent work [5] suggests that the circulating eosinophile level is "only an indirect measure of adrenal stimulation." Furthermore, urinary excretion studies have several shortcomings. Accurate measurements of short-term changes in adrenal activation are difficult to perform, owing to inaccuracies inherent in collection. Secondly, most determinations of urinary steroids measure conjugated corticosteroids instead of the unconjugated and presumably most active hormones. A more direct measure of adrenal function is afforded by estimation of circulatory corticoids. Therefore, in the present study the concentrations of plasma 17-hydroxycorticosteroids were measured directly during typhoid vaccine treatment.

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This work is part of a study done in collaboration with Dr. N. P. Christy in the laboratory of Dr. J. W. Jailer, Departments of Medicine and Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University (see *Proc. Soc. Exper. Biol. & Med.* 91:453, 1956).

Materials and Methods

The patients included in this study were 14 adult men and women, in good general health, who were admitted to the Institute of Ophthalmology for treatment of various forms of uveitis or keratitis. The typhoid vaccine was obtained from the Department of Health, City of New York. One milliliter contained 1,000,000 killed Salmonella typhosa organisms, 250,000,000 killed Salmonella paratyphi A, and 250,000,000 killed Salmonella paratyphi B organisms. In all but two of the patients the typhoid vaccine was administered by injecting intravenously 5,000,000 killed typhoid organisms (plus 1,250,000 of both S. paratyphi A and B), followed in two hours by another intravenous injection of the same dose. One patient (No. 13) received a single intravenous injection of 10,000,000 killed typhoid organisms, while the last patient (No. 14) received a continuous 12-hour intravenous infusion at 40 drops per minute of a saline solution containing 1,000,000 typhoid organisms per cubic centimeter. Rectal temperatures were taken at hourly intervals or more frequently.

Control blood specimens were obtained, and additional specimens were drawn during the course of the treatment. Plasma 17, 21-dihydroxy-20-ketosteroid levels were determined according to the modified method of Silber and Porter.* The range of normal values in this laboratory is 4γ to 28γ per 100 cc. of plasma, with a mean value of 16γ±6.9γ per 100 cc.

In four patients, after one course of typhoid vaccine and after temperatures had returned to normal, aminopyrine was given orally over a 24-hour period in doses of 0.6 gm. every four hours. On the succeeding day typhoid vaccine was again administered and blood specimens were obtained according to the above schedule. Two or three days later a third course of vaccine was given and plasma steroids were again measured.

Results

As can be seen in the accompanying Table, Patients 1-12, who received two typhoid injections, showed an abrupt rise in temperature to levels of 102.6 to 105.6 F (Table 1). In each case the temperature peak was approximately two hours after the second injection. Similarly, in every case the level of plasma 17-hydroxycorticosteroids rose abruptly from control values to values of 32γ to 59γ per 100 cc. of plasma, well above the extremes of the normal range. These

* References 6 and 7.

TABLE 1.—*Effect of Intravenous Typhoid Vaccine on Levels of Plasma 17-Hydroxycorticosteroids*

(Time in Hours After the Second Vaccine Injection)

Patient	Maximum Temperature F (2 Hr.)	Plasma 17-Hydroxycorticosteroids, γ/100 Cc.		
		Control	2 Hr.	4 Hr.
1	103.8	18	43	34
2	104.8	15	39	30
3	103.8	17	42	33
4	104	32		50
5	103	20	40	
6	102.6	16	36	
7	104.4	17	36	
8	103.8	7	32	
9	103.6	17	36	
10	102.6	18	33	22
11	104	20	43	45
12	105.6	13	46	34

peak levels are comparable to the maximum levels obtained by the standardized intravenous infusion of corticotropin (ACTH).[8] In general, the rise and fall in plasma steroid levels correlated in time with the rise and fall in temperature, the peaks of each coinciding closely. However, this relationship is not always a precise one (Chart 1).

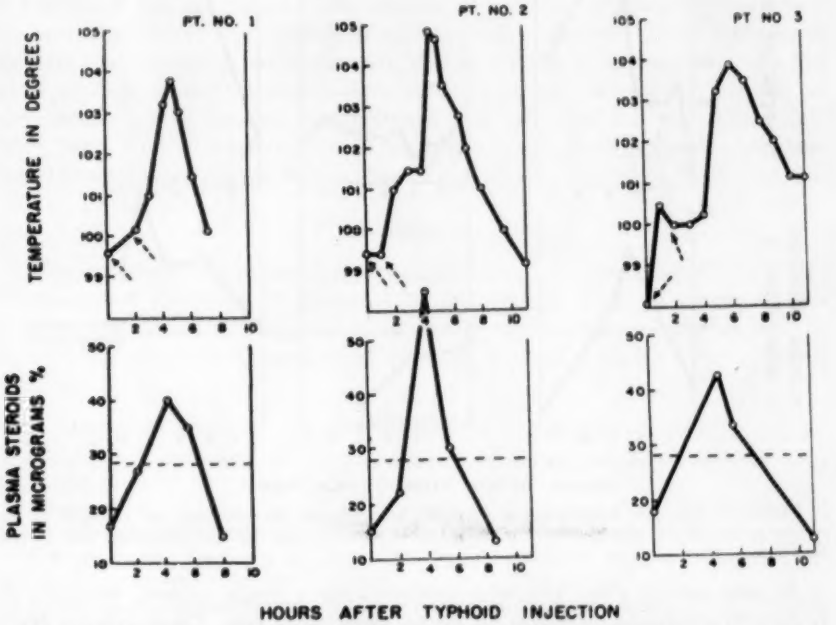

Chart 1.—The response of three patients who received 5,000,000 killed typhoid organisms intravenously and a repeat injection two hours later (see arrows). The upper graph shows the changes in concentration of plasma corticosteroids during treatment.

In four patients who received aminopyrine on the day prior to the repeat typhoid treatment, the febrile response to typhoid was dramatically suppressed (Table 1). These patients showed no rise in plasma 17-hydroxycorticosteroid levels during the typhoid vaccine administration. Despite the fact that they were afebrile, all four patients complained of constitutional symptoms (nausea, malaise, headache) two hours after the second typhoid injection. Administration of the typhoid treatment still a third time, in similar doses, without prior aminopyrine treatment, again resulted in an abrupt temperature rise associated with a rise in plasma steroids (Chart 2).

TABLE 2.—*Effect of Aminopyrine on the Plasma 17-Hydroxycorticosteroid Response to Intravenous Typhoid Vaccine*

(Time in Hours After the Second Vaccine Injection)

Patient	Maximum Temperature, F (2 Hr.)	Plasma 17-Hydroxycorticosteroids, γ/100 Cc.	
		Control	2 Hr.
1	99.4	25	24
2	99.6	14	17
3	100.4	24	22
8	99.6	20	28

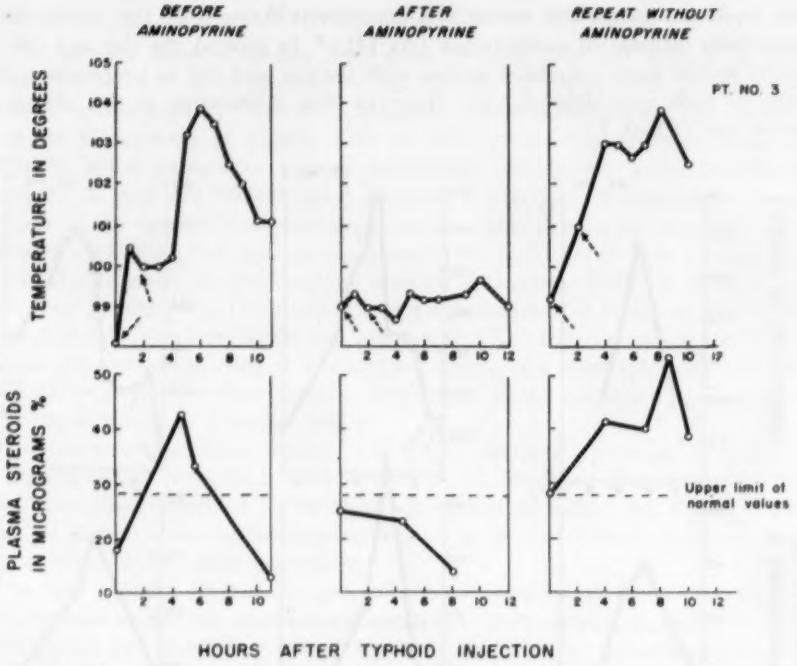

Chart 2.—The febrile response to typhoid vaccine and the simultaneous changes in the concentration of the plasma corticosteroids before aminopyrine, after aminopyrine, and several days later.

In one patient (No. 13) who received only a single typhoid injection of 10,000,000 organisms there was no abrupt temperature rise. The maximum fever of 102.8 F was reached gradually 30 hours after the injection. In this case circulating 17-hydroxycorticosteroid levels did not leave the normal range.

The last patient (No. 14), who received a continuous 12-hour intravenous typhoid vaccine infusion, maintained a temperature at levels of 103 degrees for 12 hours. During this entire period the plasma steroids remained well above the normal limits.

Comment

The demonstration that typhoid vaccine therapy is followed by an abrupt rise in plasma corticosteroids confirms the fact that this treatment activates the pituitary-adrenal axis in human subjects. The fact that the rise and fall of these plasma steroids roughly parallels the rise and fall of temperature and the fact that any increase in the circulating corticosteroids can be prevented by blocking the febrile response to typhoid vaccine suggest that fever per se is an essential factor in bringing about the activation of the adrenal cortex. It is interesting that the circulating corticosteroids remained elevated for 12 hours in the patient whose temperature was maintained at 103 F for this period. This was in contrast to the relatively brief elevation of both temperature and plasma steroid levels observed in the other patients.

An association between fever and adrenal activation, however, does not necessarily define the mechanism of action of typhoid vaccine. It is possible that other

physiologic responses such as vasodilatation, changes in the formed elements of the blood, or pyrexia itself exert a beneficial effect on certain eye diseases. In this study no attempt was made to distinguish between the clinical effectiveness of typhoid vaccine with febrile response and that of vaccine with suppression of the fever. Some clinicians claim, without documentation, that typhoid vaccine is helpful in diseases where administration of local or systemic corticosteroids has been unsuccessful, and perhaps this observation is correct. On the other hand, the fact that circulating corticosteroids, during typhoid treatment, often reached levels as high as the maximum levels obtained by the intravenous infusion of corticotropin points out that this treatment is a potent adrenal stimulator. Certainly, then, it would not seem wise to use intravenous typhoid in those cases where systemic corticosteroids are contraindicated.

Summary

The intravenous administration of typhoid vaccine to human subjects produces adrenocortical activation, as measured by increases in levels of circulating 17-hydroxycorticosteroids. Suppression of the pyrogenic effect of the vaccine by aminopyrine prevents adrenocortical response without blocking other systemic reactions.

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Ocular and Dermal Melanocytosis

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Pigmented lesions involving ocular structures are always a source of concern until proved benign. We wish to call attention to a striking pigment change, involving the eye and eyelids, which is benign but which simulates malignant disease.

Because there exists a confusion of names describing pigmentary abnormalities of the eye and surrounding structures, a new terminology is suggested. These new terms describe the presence of *ectopic* melanin-forming cells (melanocytes) in unusual sites and number in the skin and eye. The following Tabulation summarizes these proposed changes:

Present Terminology	Proposed Terminology
Melanosis bulbi	Ocular melanocytosis *
Nevus fuscocaeruleus ophthalmomaxillaris Ota	Oculodermal melanocytosis
Mongolian spot	Dermal melanocytosis

Normal pigmentation of human skin is related to the presence of melanin in highly branched cells located at the epidermal-dermal junction. The melanin-forming cells are called melanocytes, and their dendritic processes are intricately branched. The processes weave between the Malpighian cells and give the mistaken impression that Malpighian cells form melanin.

In the eye, melanin is normally found in the uveal tract and in the pigmented layers of the retina, ciliary body, and iris. Melanocytes may move into the ciliary muscle and sclera from the uveal tract. Sometimes several melanocytes accompany the vessels perforating the sclera and appear subconjunctivally as areas of pigment around the anterior ciliary vessels and nerves.

Usually no pigment is present in the conjunctiva of Caucasians except in the basal epithelium immediately around the limbus. In the darker races it is found in the basal cells of the entire conjunctival epithelium and in the episcleral tissue.

Ocular and dermal melanocytosis (melanosis bulbi, nevus of Ota) has been reported in Orientals,[3] Caucasians,[4] and Negroes.[5] It is commonest in Orientals; from 1940 to 1950, of the dermatologic outpatients of the Tohoku University, 0.5% were diagnosed as having nevus of Ota.[6] Usually, the pigmentation appears at birth, but it may be noted first at puberty or during pregnancy. Upper and

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* The term melanocytosis is derived from a combination of melanocyte, the newly accepted (References 1 and 2) term for the mature melanin-forming cell, and the suffix *-osis*, which denotes a physiological or pathological increase.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

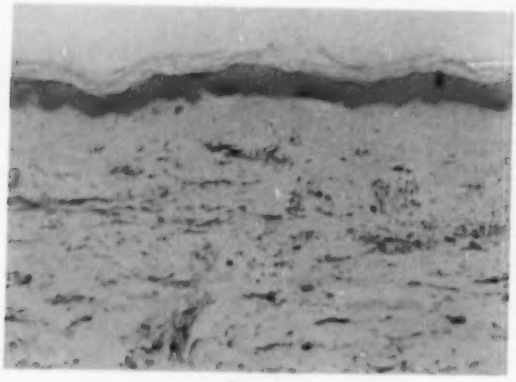

Fig. 5

Fig. 6

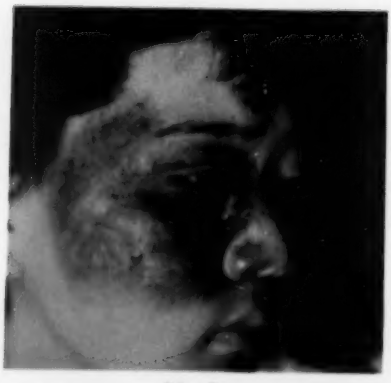

Fig. 7

Fig. 8

Fig. 9.—Scleral biopsy specimen of case of oculodermal melanocytosis, showing ectopic melanocytes in sclera.

lower lids are most commonly affected, with two-thirds of all the cases showing ocular involvement. The temples, zygomatic region, cheeks, and forehead may be involved. Frequently, the lesion is unilateral and appears to occur in areas supplied by the first and second branches of the fifth cranial nerve.

The skin lesions may be of various hues from black, slate blue, and dark brown to brown. The intensity of the skin pigmentation may vary from day to day, especially in females. The variations in color hue may be related to pituitary or ovarian hormonal stimulation of dermal melanocytes associated with various physiologic states (menses, puberty, and pregnancy).

A complete report with a review of all published cases will appear elsewhere.

Diagnosis of oculodermal melanocytosis depends on: (1) presence of pigmentation of skin of lids, cheeks, and forehead plus evidence of increased pigment of eye—usually unilateral but occasionally bilateral; (2) biopsy of pigmented skin demonstrating melanocytes in the dermis.

Fig. 1.—A 50-year-old Caucasian woman whose right upper and lower lids and the "white" of the right eye have been darker than the left side since birth. Recently noted appearance of brown patches in a previously normal area of skin in right temporal region. Two brothers and four sisters and parents show no unusual pigmentation. Functionally, both eyes were normal, showing normal visual fields and visual acuity.

Fig. 2.—Biomicroscopic examination showed brown pigment granules below the bulbar conjunctival epithelium. The sclera was definitely darker on the right.

Fig. 3.—Fundus photograph of left eye.

Fig. 4.—Fundus photograph of right eye, showing blue-gray pigmentation which contrasts sharply with the photograph of the left fundus. (The exposure used to photograph the right fundus was longer than that for the left.)

Fig. 5.—Biopsy specimen of skin taken from right temporal region of the 50-year-old white woman shows ectopic melanocytes in the dermis.

Figs. 6, 7, and 8.—More intense skin pigmentation is seen in these Japanese women. Two of the women show scleral involvement. The darker blue nodule seen on the cheek of the woman shown in Figure 7 is a blue nevus within an area of oculodermal melanocytosis (nevus of Ota).

Differential diagnosis:

(1) Precancerous and cancerous melanosis of the conjunctiva
  (*a*) Usually appears about middle age
  (*b*) Skin of lids and surrounding areas not usually involved.
  (*c*) Pigment invades cornea and is accentuated at limbus
(2) Congenital conjunctival pigmentation
  (*a*) Usually located near limbus
  (*b*) No associated skin pigmentation
(3) Diffuse "flat" nevus of conjunctiva
  (*a*) Usually elevated
  (*b*) Lesions have sharp margins
  (*c*) Microscopic picture is diagnostic

Treatment: This is a benign lesion, although malignant melanoma has been reported arising [4] in a case of oculodermal melanocytosis.

Summary

A new term, oculodermal melanocytosis, is suggested to describe a type of pigmented lesion of the skin and the eye formerly designated as nevus of Ota. The condition is benign and must be distinguished from precancerous and cancerous melanosis of the conjunctiva.

Dr. George P. Lyman, Portland, Ore., referred the patient whose photographs are shown in Figures 1-5.

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Oculocutaneous Melanosis or Nevus of Ota

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The association of a Mongolian spot of the forehead or cheek with congenital ocular melanosis is apparently a familiar entity to dermatologists, but only two case reports of this type of pigmentation have been found in the ophthalmic literature. Pusey,[1] in 1916, recorded the association of scleral and facial pigmentation in a case report of a young Chinese student. Jensen and Haffly,[2] in 1948, also reported the occurrence of ocular and dermal melanosis in a 47-year-old Chinese man. In 1930, Ota,[3] in Japan, noted a form of pigmented nevus found especially on the face and named it nevus fuscocaerulus ophthalmomaxillaris because of its blue-brown color and its frequent occurrence in the skin area of the zygomatic and maxillary divisions of the fifth cranial nerve. This syndrome of ocular and cutaneous melanosis has subsequently been reported in the dermatological literature as the nevus of Ota. We wish to report two cases and to review the literature.

Case 1.—A 7-week-old Negro girl was seen in the eye clinic of the Hospital of the University of Pennsylvania on Feb. 22, 1956, because of bluish discoloration of the sclera of the right eye and a birthmark on her right forehead. The mother stated that this pigmented lesion was present at birth and that her three other children were normal. Gestation was full term, with a birth weight of 7½ lb. No other defects were noted.

Vision appeared grossly normal, with the infant able to follow light with either eye. A large area of green-blue discoloration of the skin was present over the right frontal area in the region of the ophthalmic division of the trigeminal nerve (Fig. 1). Discrete small patches of similar blue-green pigmentation were noted also on the right upper and lower lids and the right ala nasi. The involved areas were smooth and macular in appearance and did not blanch on pressure. The sclera of the right eye (Fig. 2) presented a dark blue color and appeared to be thinned, with the discoloration due to uveal tissue showing through. With a Barkan light and corneal microscope, however, it was obvious that the sclera was deeply pigmented with melanin and otherwise of normal structure. The iris pattern and fundi were normal.

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The clinical impression at the time was Mongolian spot of the forehead with congenital melanosis oculi, and the feeling was that biopsy was not indicated. A superficial search of standard textbooks and recent periodicals revealed no similar cases. In a discussion of this case with a dermatologist, Dr. W. George Hambrick,* it was pointed out that this type of pigmentation fell in the category of nevus of Ota and we were directed to the dermatological literature.

Case 2.—A 61-year-old white man was admitted to the Veterans Hospital of Philadelphia on Feb. 23, 1956, with coronary insufficiency. Eye consultation was requested because of pigmentation of the sclera and conjunctiva. The patient related that he had always had a brownish discoloration of the left side of his face and forehead and a brown discoloration of his left eye. Neither the extent nor color of this pigmentation had changed. Ocular examination disclosed a corrected visual acuity of 6/6 in each eye. The skin of the left cheek and forehead presented a dark brown discoloration, which was smooth, macular in appearance, and not sharply delineated from the normal skin (Fig. 3).

The palpebral conjunctiva of the left eye showed several small areas of dark pigmentation. The sclera also contained discrete islands of bluish-black dis-

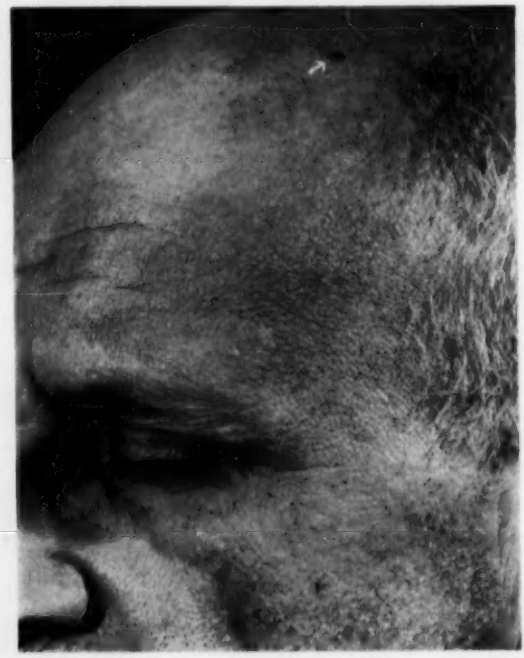

Fig. 3.—Mongolian spot of left side of face and forehead. Arrow indicates site of biopsy.

coloration typical of melanosis (Fig. 4). Heterochromia of the iris was present, with the left iris having a homogenous dark brown color while the right iris was hazel-colored (Fig. 5). Pupillary reactions were normal, and the ocular tension was 17 mm. Hg (Schiøtz) in each eye. The fundi were normal except

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Fig. 4.—Melanosis of sclera of left eye.

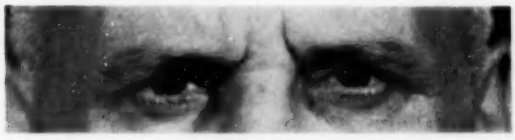

Fig. 5.—Heterochromia of left iris.

for vessel changes indicative of moderate hypertension and early arteriolar sclerosis and showed no evidence of abnormal pigmentation.

A biopsy of the skin of the forehead was taken (Fig. 6), and the microscopic report read as follows: "The epidermis is unremarkable. In the dermis are scattered pigment laden cells, most of which are plump and contain coarse,

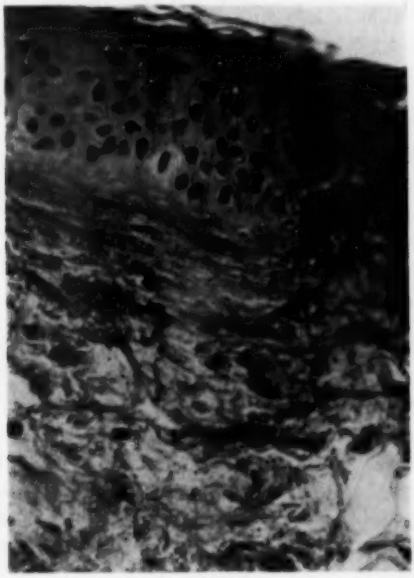

Fig. 6.—Skin biopsy specimen, showing pigment cells in dermis.

golden granules. In addition, there are many spindle shaped cells filled with brown pigment granules." The pathologist considered the type and number of pigment cells present in the dermis insufficient to warrant a diagnosis of blue nevus. He thought that the histological changes were more compatible with the diagnosis of a Mongolian spot, since the lesion had been present since birth.

The patient subsequently became icteric, and a cholangiogram showed a dilated common bile duct. A laparatomy was performed. No stones could be located, and a dilated common bile duct was the only abnormal finding. A T-tube was inserted, and the patient made an uneventful recovery.

Comment

Dorsey and Montgomery [4] state that the nevus of Ota is essentially a Mongolian spot located on the side of the face and involving the eye. The unique character of the nevus is its involvement of the sclera of the eye and deeper structures of the face, including the ocular muscles, the retro-orbital fat, and even the periosteum of the orbit. The skin lesion is usually macular, but sometimes discrete blue nevi arise within it to produce a nodular consistency.

Mongolian spots may occur on any part of the body, but they are seen most commonly in the sacral region. Subcutaneous pigmentation in the sacral area was called a Mongolian spot because it was thought to occur only in the Mongolian and Negro races. It is now known that this pigment system is observable in all races during the first year of life and that it disappears after about the fourth year. Sometimes pigmented areas, identical in appearance to the sacral Mongolian spot, are seen elsewhere on the body, and such lesions are called aberrant, or extrasacral, Mongolian spots. Mercer,† in discussing pigmentation of the skin, stated that true Mongolian spots fade while aberrant spots may have their onset later in life and extend to cover larger areas. Some of the anthropoids normally exhibit dermal and ocular melanosis, and this has furthered the thought that this type of pigmentation is atavistic.

The cells in a Mongolian spot are identical with blue nevus cells and give a positive dopa reaction. They are characteristically spindle-shaped bipolar dendritic cells located in the lower two-thirds of the cutis and separated from the overlying epidermis by normal cutis. These cells are spaced widely in the dermis and do not disturb the normal architecture of the skin, while the cells in the blue nevus occur in clumps and wavy groups. The histopathologic picture of the nevus of Ota varies from that of a Mongolian spot to that of a cellular blue nevus. Blue nevi and Mongolian spots are both seen more commonly in persons of dark-skinned races.

The nevus of Ota is common in Japan, where Tanino,[6] in 1940, reported 26 cases and Yoshida,[7] in 1952, reported 110 cases. Yoshida could establish no evidence of inheritance. In only one instance was the mother and a cousin similarly affected. Nearly half of the Mongolian spots were located in the cutaneous area of the ophthalmic division of the trigeminal nerve. The extent of melanosis oculi varied from an almost completely blue sclera to that in which pigmentation was millet grain in size. Bourquin,[8] in describing congenital melanosis oculi, in 1917, listed the following changes which may be present: excessive pigmentation of the iris; dark iron-gray color of the fundus; pigmentation of the conjunctiva; discoloration of the sclera; pigmentary deposits in the

† Mercer, S. R., in discussion on Cole.[5]

optic papilla, and discoloration of the lid. Any or all of these pigmented changes may be present as the ocular component in the syndrome of oculocutaneous melanosis.

Nine cases previously reported under the suspicion of blue nevus, Mongolian spot, or argyria seem to be the nevus of Ota in view of the type and location of the pigmentation.† Cole, Hubler, and Lund [10] also reported four patients with persistent aberrant Mongolian spots, among which was the case of progressive ocular melanosis previously reported by Jensen and Haffly.

Oculocutaneous melanosis is generally considered benign and harmless except from a cosmetic viewpoint. Dorsey and Montgomery,[4] however, have reported two patients in whom malignant change has occurred. One was a young woman of 24 years with a malignant melanoma arising on the left temple within the nevus of Ota. The second was a 16-year-old boy with a nevus of Ota on the right side of the face from which developed a malignant mass eroding into the right maxillary sinus. They state that malignancy has never been reported in a Mongolian spot, and no incidence of malignant change in a nevus of Ota can be found prior to their report.

Comment

The onset of ocular and cutaneous pigmentation is generally noted at birth, as it was in our two cases. It may, however, have its onset in later life and be progressive, as was reported by Jensen and Haffly.[2] These lesions are commoner in members of the dark-skinned races, but Caucasians are not spared. It is well known that pigmented nevi and hemangiomas are frequent in the skin of the zygomatic and maxillary divisions of the trigeminal nerve. Both cases in this report have typical extrasacral Mongolian spots localized to this area. The ocular involvement in the infant was melanosis of the sclera, with no other evidence of abnormal ocular pigmentation. The skin lesion in the infant was not biopsied.

The second patient denied any change in the degree or extent of his pigmented lesions. In addition to the Mongolian spot on the left side of his forehead, he had melanosis of the sclera and conjunctiva and marked heterochromia of the iris of his left eye. There was no evidence of abnormal pigmentation in the fundus, and biopsy of the skin showed spindle cells in the dermis consistent with the diagnosis of Mongolian spot. No evidence of malignant change was present in either case. This syndrome is rare, since only 16 cases have previously been reported in the American literature.

Although eponyms are generally undersirable, the term "nevus of Ota" has previously been used in the dermatology literature to denote this entity of ocular and cutaneous pigmentation. Since the pigmentation is due to dermal melanoblasts and nevus cells are not found in the lesions, the term "oculocutaneous melanosis," suggested by Jensen and Haffly,[2] would be more appropriate for the syndrome.

Summary

Two cases of oculocutaneous melanosis, or nevus of Ota, are reported, one in a 7-week-old Negro infant and the other in a 61-year-old white man. The literature on the association of ocular and dermal pigmentation is reviewed. The

‡ References 9-17.

term "oculocutaneous melanosis" is preferred to the eponym of "nevus of Ota" as the name for this syndrome.

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Fig. 1.—Mongolian spot on the right forehead, lids, and ala nasi.

Fig. 2.—Melanosis of sclera of right eye.

Primary Congenital Entropion

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Primary entropion is an uncommon congenital anomaly. It is much rarer than the secondary type of congenital entropion, which is usually associated with anophthalmos, microphthalmos, epiblepharon, etc. In these secondary cases the cause is usually mechanical and is due either to (1) lack of support to the lid margin by a small or absent globe or (2) backward pressure on the ciliary margin by an excess fold of skin, as in epiblepharon. By definition, then, primary congenital entropion is usually seen in eyes with otherwise normal globes and adnexa.

The importance of this anomaly is in the injury which might be caused to the cornea by the inversion of the margin and lashes. The treatment is always surgical.

A total of 22 cases * of primary congenital entropion has been found in the literature to date. The statistics of these cases are interesting, though not particularly enlightening: Approximately two-thirds of the patients were females; one-third were males. One [4] had entropion of both upper lids; one,[1] of both upper and left lower lids; four † had only one lower lid involved. The other 16 showed entropion of both lower lids. In one case [14] inversion of the lid margin was due to an accessory row of Meibomian glands. In five cases ‡ entropion was due to absence or deficiency of the tarsus. The others were attributed to hypertrophy of the marginal or tarsal fibers of the orbicularis muscle.

This is a report of two cases of primary congenital entropion occurring in two female siblings.

Report of Cases

Two sisters aged 2 years 8 months and 1 year 8 months, respectively, were first seen in July, 1955. The mother stated that she first noticed the lids of the older child turning in when she was 7 or 8 months old. When this was called to the attention of the attending pediatrician he thought that the condition would correct itself "when the baby fat in the cheeks disappeared." However, since then the condition in both eyes has become aggravated.

Examination of the older child disclosed an obvious entropion of both lower lids. The conjunctivae of the lower fornices were chemotic, and there was mucoid discharge from both eyes with occasional tearing. The child had acquired the habit of pulling the lower lids down in order to diminish irritation. The eyes were quite normal in all other respects (Fig. 1*A*).

Examination of the younger child also showed an early bilateral entropion of both lower lids. However, signs of conjunctival irritation were minimal. There were no other anomalies of either eye (Fig. 1*B*).

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From the Department of Ophthalmology, Goldwater Memorial Hospital.

* References 1-15.

† References 7 and 12-14.

‡ References 3, 4 and 12.

Fig. 1.—Primary congenital entropion of both lower lids in two female siblings. *A*, 2 years and 8 months old; *B*, 1 year and 8 months old.

Fig. 2.—Postoperative appearance of the older child.

The right entropion of the older child was repaired on Sept. 15, 1955, by the excision of a strip of skin and muscle. The left entropion was repaired in similar fashion on Oct. 28, 1955. The final result is shown in Figure 2. The younger child has not required surgery to date.

Comment

It is not always easy to distinguish clinically between congenital entropion and epiblepharon, and the literature bears witness to this. Indeed, a glance at the reference titles § will show that a few of the cited cases are possibly not "pure" cases of primary congenital entropion, i. e., those of Denig,[5] von Herrenschwand,[8] and Czukrász.[15] However, a reading of the reports would seem to indicate that they fit this category best, and they have therefore been included here.

Duke-Elder [16] defines epiblepharon as "a developmental anomaly characterized by the presence of a fold of skin running horizontally across the upper (epiblepharon superior) or lower lid (epiblepharon inferior)." Occasionally there may be two or even three skin folds.

In general it may be said that the main difference between these two clinical entities is the position of the lid margin which, as in all cases of true entropion, is inverted along its entire length in cases of congenital entropion. In epiblepharon it is the lashes only which are pushed against the globe. Another clinical difference is that epiblepharon occurs relatively more commonly and tends to disappear by the end of the first year and therefore rarely requires surgery. This is not true of the rarer congenital entropion, which becomes aggravated with growth and always requires surgical intervention. For this reason it is always best to watch the newborn infant for several months, and preferably to the end of the first year, before undertaking surgery. Von Herrenschwand,[17] in discussing the differential diagnosis, points out that in congenital entropion the tarsus is pulled out of position owing to relative overaction of the marginal fibers of the orbicularis. (This is not unlike the common senile entropion of the adult.) On the other hand, in epiblepharon it is the skin of the lid which bulges out and pushes the cilia against the globe, especially in downward gaze. He suggests that this may be due to some anomalous connection between the skin and the inferior rectus muscle.

Summary

Two cases of primary congenital entropion are reported.

Primary entropion is a rare congenital anomaly, of which reports of only 22 previous cases have been found in the literature. It occurs most frequently in female children and in both lower lids.

The commonest cause is hypertrophy of the marginal fibers of the orbicularis. A less frequent cause is absence or deficiency of the tarsal plate.

Congenital entropion must be differentiated from epiblepharon. In the former the whole lid margin is inverted and it tends to become aggravated with the passage of time. Epiblepharon is characterized by an accessory fold of skin which pushes the cilia against the globe. It tends to disappear by the end of the first year.

Congenital entropion always requires surgery. It is readily amenable to the simple excision of enough skin and muscle to cause eversion of the lid to a normal position.

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Malignant Melanoma of the Choroid

A Correlation of Clinical and Histological Findings

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Some cases of malignant melanoma of the choroid pose little or no problem in diagnosis. However, in other cases, after all available diagnostic procedures have been used, only a presumptive clinical diagnosis can be made. The decision for enucleation then must rest on clinical judgment and consideration of the risk involved in watchful waiting, especially in an eye with useful vision.

To discover clinical criteria which might be of help in making a differential diagnosis, a survey was made of the melanomas received at the pathology laboratories at the Illinois Eye and Ear Infirmary and the Research and Educational Hospitals of the University of Illinois. The clinical descriptions were studied, and an attempt was made to correlate them with the histologic picture. Those cases in which the eye was enucleated because of the possibility of a melanoma and in which, on histologic examination, no tumor was found, will be presented to show some of the commoner conditions to be considered in differential diagnosis.

In this series are 228 cases of malignant melanoma of the choroid. Melanomas of the anterior segment and other types of tumors were excluded. In 24 of these eyes, the tumor was discovered in the laboratory and was not suspected clinically. Eighty-one eyes were enucleated because of the possibility of melanoma and were found not to contain tumors.

Characteristics of Tumors

In Table 1 are listed some of the clinical characteristics of these tumors with

TABLE 1.—*Clinical Characteristics of Malignant Melanoma of the Choroid*
(74 Cases)

	Per Cent
Tumor in vitreous	3
Solid tumor	46
Solid tumor plus serous detachment	39
Serous	11
Serous with retinal tear	1

or without associated "serous" retinal detachments which were encountered in this series. The tumor had broken through the retina to grow freely in the

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vitreous in 3% of the cases. Forty-six per cent of the cases were described as solid tumors. However, histologically, small serous detachments were found along the edge of many of the larger solid tumors. Thirty-nine of the cases were described clinically as solid plus serous detachments. In 11% of the cases only a large serous retinal detachment was visible. A retinal tear was described in only one eye containing a melanoma.

Figure 1 shows a large solid tumor without serous detachment. Clinically, a

Fig. 1.—Solid detachment.

Fig. 2.—Flat melanoma with extrabulbar extension.

smooth surface is presented without retinal folds. The retina is relatively immobile on movement of the eye rather than undulating or tremulous. The edges of the tumor are distinct and, in this relatively late stage, there is a steep slope from the crest of the tumor. Being heavily pigmented and without any overlying fluid, this tumor appears solid and black on ophthalmoscopic examination. Transillumination does not appear on the side of the tumor.

The shape and elevation of tumors varies greatly. Figure 2 shows a very flat tumor which has already spread extrabulbarly to involve an extraocular muscle. The first clinical manifestation of such tumors may be a paresis of an extraocular muscle or an exophthalmos. The differential diagnosis of these flat melanomas may be difficult. Metastatic carcinoma tends to remain flat as it spreads throughout the choroid. Choroiditis or subretinal hemorrhage may give a similar picture.

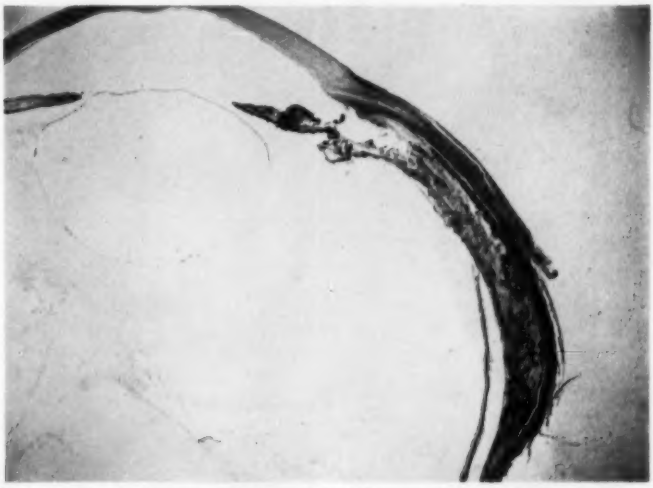

Fig. 3.—Flat melanoma which was first diagnosed syphilitic chorioretinitis.

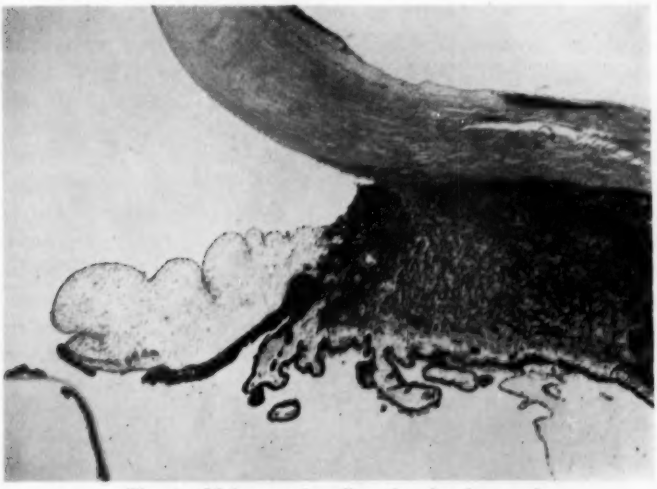

Fig. 4.—Melanoma invading the chamber angle.

Figure 3 shows a flat melanoma which was first thought to be syphilitic chorioretinitis. The eye was treated and observed for some time before the proper diagnosis was made and the eye enucleated. When a melanoma of the anterior choroid or ciliary body extends into the root of the iris and fills the chamber angle (Fig. 4), the diagnosis can often be made early by the use of the gonioscope. If the involvement of the angle is over a broad area, these eyes soon become glaucomatous.

Pigmentation in melanomas varies greatly. The tumor may be heavily pigmented and appear black or brown (Figs. 1 and 5). The melanoma shown in

Fig. 5.—Heavily pigmented melanoma.

Fig. 6.—Melanoma containing very little pigment.

Fig. 7.—Melanoma containing heavily pigmented and nonpigmented areas.

Figure 6 contains very little pigment and would give a slate-gray appearance which closely resembles a gray-white serous retinal detachment. In other melanomas the pigment runs in streaks or clumps and gives a mottled appearance to the tumor. Figure 7 shows heavily pigmented areas adjacent to nonpigmented areas in the same tumor.

Melanoma Associated with Serous Detachment

The presence of a serous detachment adds to the difficulty in diagnosis of a malignant melanoma of the choroid (Fig. 8). The serous detachment may completely surround the tumor, but it is usually more pronounced on the dependent side of the tumor. The tumor is usually in contact with the retina at the highest point of elevation, and retinal striae may radiate from this apex. Ophthalmoscopically, we are actually observing the tumor through the retina at the highest point of elevation in these cases, and, surrounding this, there is a gray zone of serous detachment. A retinal elevation which does not extend to the periphery is strong evidence that the elevation is due to tumor rather than a simple detachment. A small tumor out in the periphery of the fundus will sometimes have a large serous detachment posterior to it, and the tumor may be overlooked (Fig. 9). The importance of examining the far periphery of the fundus is obvious. A small tumor may be buried deep under a serous detachment (Figs. 10 & 11), at times making the diagnosis extremely difficult.

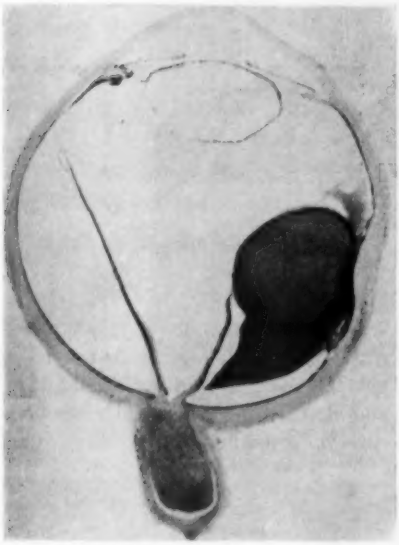

Fig. 8.—Solid plus serous retinal detachment.

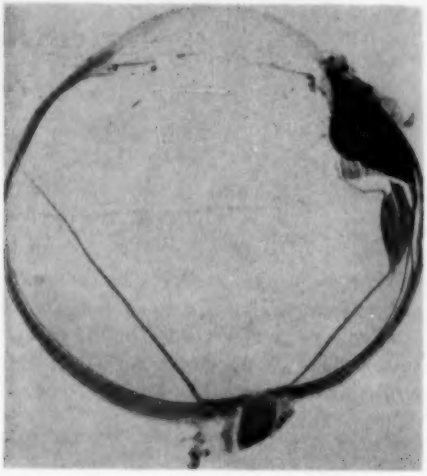

Fig. 9.—Serous detachment of the retina posterior to a small melanoma in the far periphery of the globe.

Cystoid degeneration of the retina (Figs. 6 & 12) overlying a tumor will sometimes create confusion in diagnosis. It is not uncommon to have cystoid spaces occurring in old simple detachments. Old blood or hemosiderin in these cystoid spaces may give a bulky shape to the retina and even interfere with transillumination.

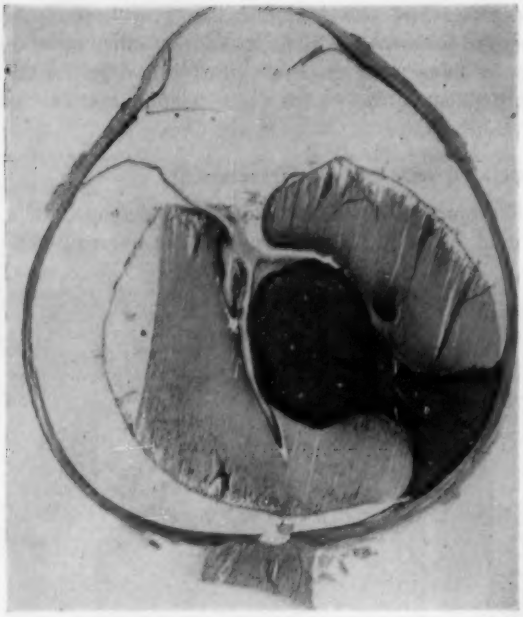

Fig. 10. — Mushroom-shaped melanoma surrounded by a total retinal detachment.

Glaucoma

Tensions were recorded in 143 cases (Table 2). The tension was found to be soft in 11% of the cases, normal in 41%, and elevated in 48%. Much has been written concerning the cause of glaucoma in eyes containing melanomas. Our

Fig. 11.—Melanoma buried deep under a total retinal detachment.

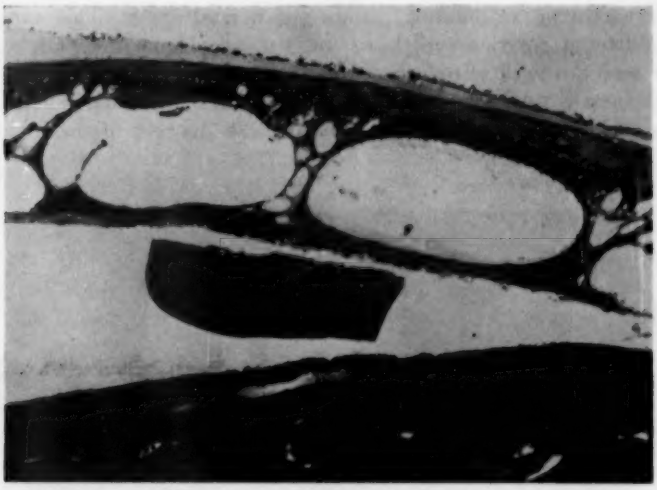

Fig. 12.—Cystoid degeneration of the retina overlying a melanoma.

findings on possible cases of glaucoma have proved to be very interesting (Table 3).

Of the 62 * glaucomatous eyes containing melanomas, 92% were found to have the angle of the anterior chamber blocked by peripheral anterior synechiae. The tumor invaded the angle sufficiently to cause glaucoma in 5% of the cases.

TABLE 2.—*Ocular Tensions*

(143 Cases)

	Per Cent
Less than 15 mm.	11
16 to 30 mm.	41
Greater than 30 mm.	48

TABLE 3.—*Cause of Glaucoma*

(62 Cases)

	Per Cent
Peripheral anterior synechiae	92
Tumor in angle	5
Sclerosed trabeculum	1
Debris (inflammatory)	1
Normal angle	0

In one case, the trabeculum was nonfunctioning because of marked sclerosis. In one eye, which was removed with a diagnosis of chronic uveitis and secondary glaucoma, the trabecular spaces were filled with inflammatory cells and debris. We did not find a normal open angle in any of these eyes. Only one was described

* Although there were 69 glaucomatous eyes containing melanomas, only 62 of these were available or adequate for histologic study.

clinically as having an anterior chamber of normal depth. This exception had broad peripheral anterior synechiae, and so undoubtedly the periphery of the chamber was narrowed. From these findings, it appears that glaucoma associated with melanoma is caused by mechanical obstruction of the trabeculum. Figure 13 shows a typical peripheral anterior synechia with the root of the iris completely closing the chamber angle.

Uveitis

Inflammation is common in eyes harboring melanomas. Fifty-two per cent of 99 eyes were described clinically as showing active uveitis or posterior synechiae. Histologically, posterior synechiae were found in 75% of 197 cases.

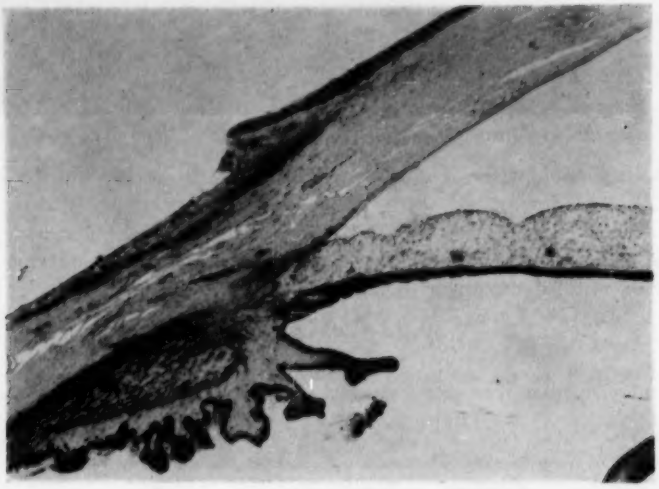

Fig. 13.—Peripheral anterior synechiae.

Tumor necrosis seems to be a probable factor in the production of uveitis in these eyes, as shown by the fact that 97% of the cases with necrosis showed histological signs of inflammation (Table 4). Two cases with very small necrotic areas did not show uveitis. Sixty-five per cent of those cases without necrosis also showed histological evidence of uveitis. Figure 14 shows a necrotic area in a melanoma. The darker staining, viable tumor cells are seen on the left.

The ocular tension was recorded in 143 eyes containing melanomas (Table 5). Of the cases with elevated tension, 94% showed histologic evidence of uveitis, while 52% of the eyes with normal tension showed uveitis. Clinically, however, uveitis was noted in 82% of those cases with glaucoma and only 20% of those with normal tension. It certainly appears that there is a causal relationship here. A plausible sequence of events might be that necrosis of the tumor results in uveitis with the formation of anterior and posterior synechiae and the development of secondary glaucoma. From our data, no evidence supports the theories that glaucoma associated with malignant melanoma is caused by either space-occupying encroachment of the tumor on the vitreous cavity or pressure on the vortex veins.

TABLE 4.—*Uveitis vs. Tumor Necrosis*

Necrosis	Cases, No.	Uveitis, % of Cases
Present	66	97
Absent	141	65

Fig. 14.—Melanoma which is necrotic on the right and contains darker-staining, visible tumor cells on the left.

TABLE 5.—*Relationship Between Tension and Inflammation in Malignant Melanoma*

Tension	Uveitis, % of Cases	
	Clinically	Histologically
Elevated	82 (44 cases)	94 (62 cases)
Normal	20 (46 cases)	52 (58 cases)

Transillumination

The results of transillumination were reported in 108 of our cases (Table 6). In 88% of the cases, the transillumination was reportedly impaired; in 5% the results were doubtful, and in 7% the transillumination appeared to be normal. Comparing the results of transillumination in solid plus serous detachments and solid detachments alone gave almost identical results. This is a very high batting average and probably places more value on this test than is justified. The interpretation of transillumination may be prejudiced by other findings suggestive of tumor. In the cases diagnosed erroneously, i. e., no tumor was present, transillumination was reported to be impaired in 44% of 18 cases. Some of these cases will be shown later to illustrate a few of the pitfalls with which this test is fraught.

Nevi of Iris

Benign melanomata in the iris of the involved eye were reported clinically in 8% of our cases, a figure closely corresponding to the findings of Reese, who considers this an important clinical adjunct. Histologic examination of 199 eyes

TABLE 6.—*Transillumination*

(108 Cases)

	Per Cent
Impaired	88
Doubtful	5
Normal	7

revealed benign nevi in the iris of 42% of the cases. Many of these nevi were small and could be easily overlooked clinically. Wilder reported benign melanomas present in the iris of 67% of the eyes containing malignant melanomas of the choroid and in 50% of other eyes. She further reported that the benign nevi seen in eyes with malignant melanoma tend to be larger than those seen in eyes

Fig. 15.—Benign melanoma of the iris.

not containing tumors. Figure 15 shows a typical, rather large benign melanoma on the anterior surface of the iris. A cross section of such a tumor is shown in Figure 16.

Dilated Iris and Scleral Vessels

Another helpful, though infrequent, sign of malignant melanoma is the presence of locally dilated iris or scleral vessels (Fig. 17). In our series, 7% (8 cases) showed locally dilated vessels of the iris, and 11% (14 cases) showed dilated scleral vessels in the area of the tumor.

Diagnostic Surgical Procedures

Diagnostic diathermies or sclerotomies are sometimes done in an attempt to flatten the retina when the presence of a tumor cannot otherwise be ruled in or out. The following case makes one stop and think before using the procedure. A 55-year-old white man complained of a shadow coming down from above and blurring of vision in his left eye for one month. A large, slightly movable retinal detachment was seen in the inferior temporal quadrant. No settling of the detachment resulted after two weeks of bed rest, and so a cautery puncture was done,

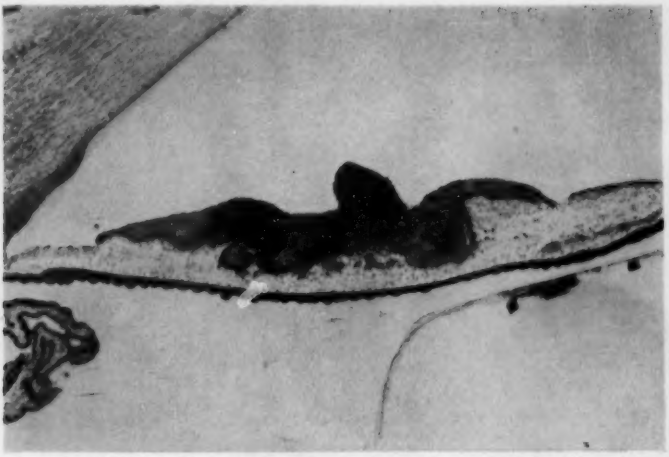

Fig. 16.—Cross section of a benign melanoma of the iris.

which yielded no fluid and did not reduce the size of the detachment. Two weeks later a second diathermy operation was done, with even more vigorous attempts to flatten the retina. Vitreous was obtained in one place but no subretinal fluid. Failure of the retina to flatten and poor transillumination in this area finally resulted in the correct diagnosis of malignant melanoma. Figures 18 and 19 show

Fig. 17.—Dilated scleral vessel.

areas in which two diathermy punctures entered the tumor. In some sections tumor cells could be seen in the diathermy tracks. It certainly seems undesirable to do a diagnostic scleral puncture unless early enucleation is performed in case subretinal fluid is not obtained or the retina does not flatten out.

Undiagnosed Melanomas

Routine histologic examination of eyes revealed 24 melanomas which were not suspected clinically (Table 7). The clinical diagnosis in these cases was glaucoma with cloudy media in 18 cases, phthisis bulbi in 3 cases, and retinal detachment in 3 cases.

Fig. 18.—Diathermy punctures entering melanoma.

Fig. 19.—Higher magnification of diathermy punctures entering melanoma.

In order to come to an intelligent diagnosis regarding a suspected intraocular tumor, one must be familiar with the conditions which may simulate or obscure a melanoma of the choroid.

Suspected Melanomas (Misdiagnosed)

There were 81 cases of clinically suspected melanomas in which a tumor was not found on histologic examination. This figure is alarming until we realize that most of these eyes did not have useful vision. The conditions found in all 81 eyes are listed in Table 8. The photographs of cases which were misdiagnosed as melanomas will demonstrate some of the conditions which must be differentiated from melanomas. The media were clear in all of these cases, and so the lesions could be seen and described clinically.

Figure 20 is an early Kuhnt-Junius, or disciform, macular degeneration, consisting mostly of fresh hemorrhage with a small area of fibrosis. Figures 21 and 22 show old, fibrotic Kuhnt-Junius types of macular degeneration in two eyes which were removed with a diagnosis of melanoma.

TABLE 7.—*Clinical Diagnosis in Undiagnosed Melanomas*

Clinical Diagnosis	Eyes, No.
Glaucoma and cloudy media	18
Phthisis bulbi	3
Retinal detachment	3

Figure 23 shows a case which was first diagnosed as a simple retinal detachment. After a diathermy procedure, the detachment had a more solid appearance

and transillumination was impaired, and so the eye was removed with a diagnosis of melanoma. A subretinal hemorrhage was found histologically. It is believed that the subretinal hemorrhage resulted from the diathermy procedure.

Figure 24 is the eye of a patient who first complained of a visual field defect. There was some vitreous hemorrhage in the area of the tumor which partially

TABLE 8.—*Cases Misdiagnosed as Malignant Melanoma*

Diagnosis	No.
Glaucoma with hazy media	24
Hemorrhage	
Subretinal or choroidal	11
Kuhnt-Junius (disciform) degeneration	3
Coats' disease	1
Inflammation	
Uveitis	10
Endophthalmitis	5
Serous detachment and glaucoma	8
Serous detachment without glaucoma	8
Cysts: iris, retinal, and Cysticercus	3
Benign pigment	3
Other tumors	
Astrocytoma	1
Metastatic carcinoma	1
No tumor	3

obscured the view. The Lancaster transilluminator showed an area of poor transillumination, and so the eye was enucleated and found to contain only a subretinal hemorrhage. The subretinal hemorrhage shown in Figure 25 was described clinically as having a greenish-gray appearance and considerable scattered black pigment. A melanoma was suspected. Figure 26 shows an old organized subretinal hemorrhage which was first discovered on a routine eye examination. It

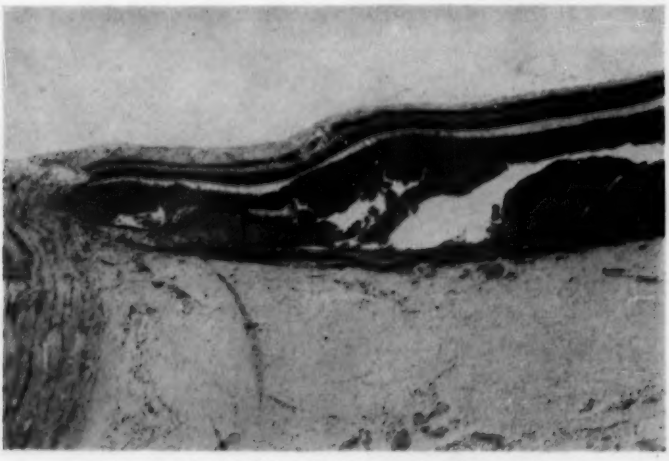

Fig. 20.—Early Kuhnt-Junius macular degeneration.

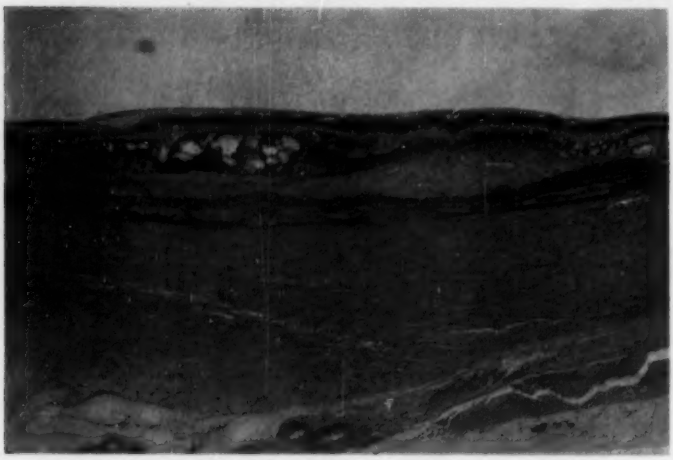

Fig. 21.—Old, fibrotic Kuhnt-Junius macular degeneration.

Fig. 22.—Old Kuhnt-Junius macular degeneration with clump of black pigment.

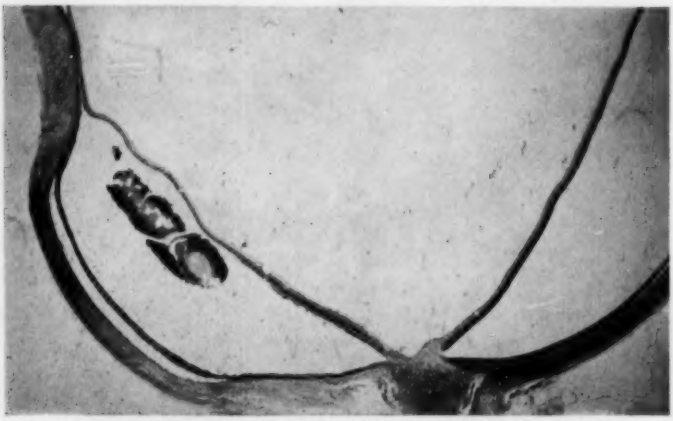

Fig. 23.—Subretinal hemorrhage after diathermy.

would be next to impossible clinically to differentiate this organized hemorrhage from a melanoma.

The eye shown in Figure 27 contained three discrete heavily pigmented lesions which were visible ophthalmoscopically. When the eye was enucleated with a diagnosis of melanoma, the tumors were found to be accumulations of large round pigment cells separating the rods and cones from the normal retinal pigment epithelium. The origin of these cells is not clear.

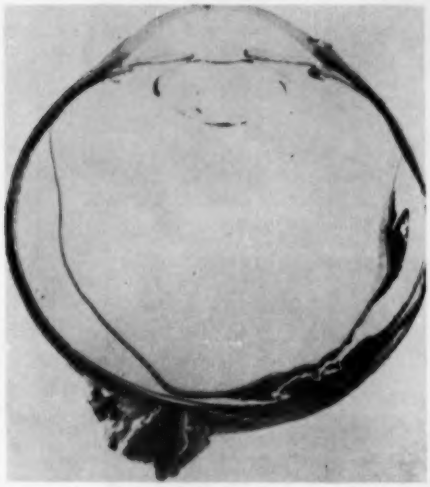

Fig. 24.—Subretinal hemorrhage.

Figure 28 shows the posterior segment of an eye which was removed with a diagnosis of malignant melanoma. A total retinal detachment was present. The retina formed a tumor mass anterior to the optic disc which was benign and, for lack of a better name, has been called a retinal dysplasia.

Fig. 25.—Subretinal hemorrhage.

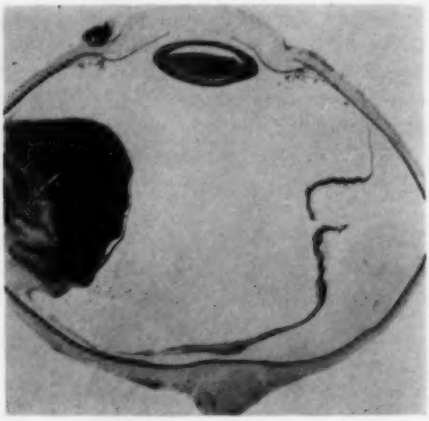

Fig. 26.—Old, organized subretinal and choroidal hemorrhage.

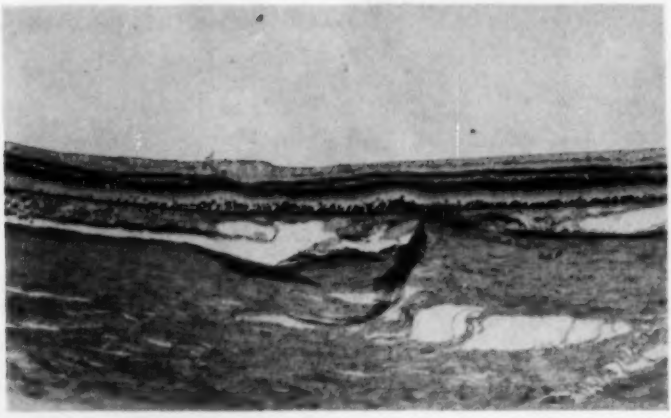

Fig. 27.—Benign pigment between rods and cones and the normal retinal pigment epithelium.

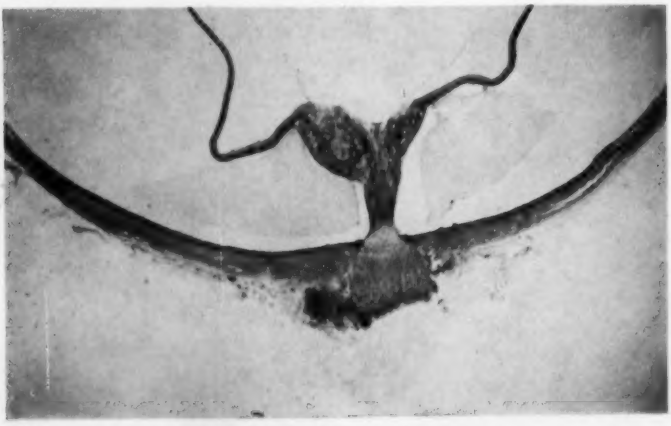

Fig. 28.—Benign retinal tumor.

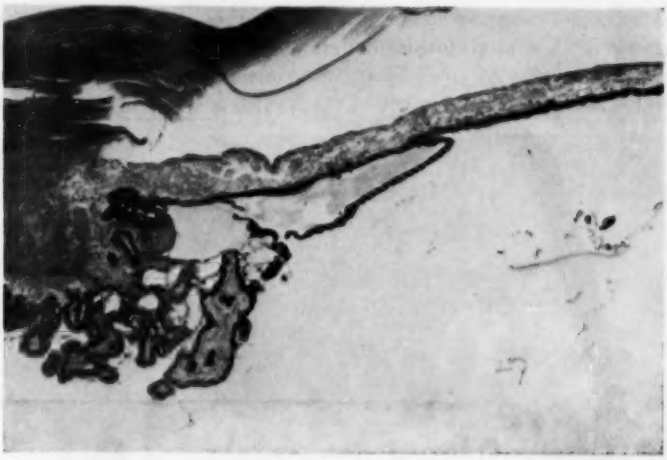

Fig. 29.—Cyst of the pigment epithelium of the iris.

The eye shown in Figure 29 was thought to contain a melanoma of the ciliary body. A pigmented tumor which distorted the pupil was visible behind the iris. Histologic examination revealed this cyst of the pigment epithelium of the iris.

Figures 30 and 31 show under low and high magnification a rare condition which must not be completely ignored when making a differential diagnosis of intraocular tumors. This is a subretinal Cysticercus.

Fig. 30.—Subretinal Cysticercus.

Summary

A series of 228 cases of malignant melanoma of the choroid are described, with correlation of the clinical and histologic findings. Twenty-four of these

melanomas were not diagnosed clinically. In addition, 81 eyes which were enucleated because of a clinical suspicion of malignant melanoma are presented to illustrate some examples of conditions to be considered in differential diagnosis.

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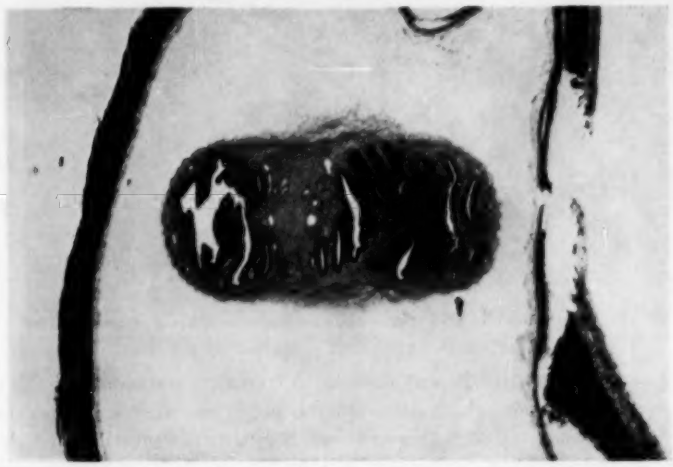

Fig. 31.—Higher magnification of subretinal Cysticercus.

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Increase of Residual Protein of Bovine Vitreous During Growth of the Eye

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It seems to be accepted [1] that if the volume of the eye increases during pathological growth, such as in myopia, the increased space is not filled with normal gel-like vitreous but rather with a "liquid vitreous." Our interest has been to determine whether, during normal growth, the increased volume of the eye is occupied by a gel-like vitreous or by the secretion of a "liquid vitreous" into a preformed residual protein structure. It has been reported by Bembridge and Pirie [2] that the rabbit probably commences to secrete hyaluronic acid into the vitreous only after birth. Balazs [3] indicates that the vitreous hyaluronic acid and ascorbic acid contents parallel the increase in the vitreous during growth, while calcium and the soluble proteins of the vitreous decrease slightly from birth to adulthood. Information is not available pertaining to the rate of formation of the residual protein.

This report attempts to correlate the quantity of residual protein in the vitreous humor with the increase in weight of the bovine eye at different age levels. The amount of residual protein in pooled bovine vitreous has been reported as 17 mg/100 cc. for the entire vitreous body.[4] The amount recorded in various portions of the vitreous (central, peripheral, anterior) has varied between 13 and 21 mg/100 cc.[5] We are presenting additional data on residual protein weights in pooled bovine vitreous, as well as on the residue weights determined on individual eyes from various age groups. The significance of the data on single eyes is evaluated statistically.

Experimental Procedure

Bovine eyes were obtained and used within two hours after death. They were collected from animals representing four age groups: 2-month premature calves, 2-week-old calves, 2-year-old steers, and 6- to 8-year-old dairy cows.

Each eye was carefully freed of loose extraocular tissues and weighed. The vitreous was then isolated as follows: An equatorial incision was made through the sclera completely around the eye, and, with a flat blade, the cornea and sclera

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were detached from the anterior uveal tissues and removed. Both the choroid and retina were then incised circumferentially. Gentle suction was applied to the lens with a rubber suction cup, and the lens-vitreous preparation was lifted away from the remaining retina, choroid, and sclera. Any remnants of retina and uvea adhering to the posterior part of the vitreous were removed by rinsing with a stream of distilled water. The vitreous was cut through 2 to 4 mm. posterior to the lens in order to avoid inclusion of zonular fibers with the sample. This vitreous preparation was weighed.

Residual protein was collected by centrifugation of these preparations at 35,000 rpm for one and one-half hours in a Spinco ultracentrifuge. The residues were then treated twice with hyaluronidase * (100 turbidity-reducing units (TRU)/ml. in 0.1 N acetate buffer, pH 5.4, in 0.15 N sodium chloride) for 16 hours at 37 C and were then finally washed thoroughly with distilled water. This treatment was previously found by us to be adequate for the removal of the hyaluronic acid and the water-soluble components on the basis of obtaining a weight which is constant both toward further hyaluronidase treatment and to further washing. The residues were air-dried at room temperature on methacrylate (Lucite) plates. The dry residues, in the form of thin sheets, were scraped easily from the plastic. They were then dried in individual desiccators at atmospheric pressure for 24 hours over an anhydrous calcium sulfate preparation (Drierite) and were rapidly weighed. It should be noted that these residues were found to be extremely hygroscopic and increased approximately 20% over their dry weights, when equilibrated in open air.

Results

The accompanying Table summarizes the results of these experiments. With each increase in the age of the group the total weight of the eye becomes greater.

Residual Protein of Bovine Vitreous During Growth

Eyes	No. in Group	Mean Wt. of Globe, Gm.	Mean Wt. of Vitreous, Gm.	Mean Wt. of Residual Protein, Mg.	Mean Mg./100 Cc. of Residual Protein in Vitreous
Unborn calves	6	9.27±1.15	3.83±0.54	0.275±0.085	7.22±1.90
Two-week-old calves	17	14.9±1.11	6.45±0.34	0.505±0.047	7.81±0.64
	9		6.5 ±0.67	0.55 (pooled)*	8.5
	17		6.8 ±0.65	0.61 (pooled)	9.0
Steers 2 years old	12	26.8±0.89	11.2±0.66	0.92±0.095	8.16±0.82
	7		10.5 ±1.41	1.04 (pooled)	9.9
	6		11.1 ±0.35	1.07 (pooled)	9.6
Cows 7 years old	11	30.0±2.12	11.15±1.75	1.01±0.18	9.00±1.76

* In the pooled samples the weight given is per eye (pooled weight/number of eyes).

The weights of whole vitreous and of the residual protein were found to increase only during the period of growth. There was found to be no change in these weights in the interval between the second and seventh years.

* Provided by Dr. Joseph Seifter, of Wyeth, Inc.

It was observed that during the sectioning of the cow eyes a liquid escaped. Both the vitreous and residual protein weights of these eyes are no different from those of the younger steers; therefore, this fluid probably accounts for the heavier globe, and it may be analogous to the "liquid vitreous" observed in elderly humans.

Statistically, any weight in any age group in the Table is significantly different from a corresponding weight in another age group, except that the weights of vitreous and residual protein for cows and steers are not significantly different.

Comment

If "liquid vitreous" were secreted into a preformed residual protein structure during normal growth of the eye, we would expect to find no increase in the amount of residual protein during the growth period. This would result in a changing ratio of residual protein to vitreous humor weight during growth.

Although there seems to be an increase in the ratio of residual protein weight to vitreous weight, as shown in Column 6, Table, statistical analysis [6] shows that, at 99% confidence limits, the values are not significantly different. The constant concentration of residual protein in the vitreous through the various stages of growth demonstrates that it is being formed at a rate consistent with growth of the whole vitreous. This suggests that all the vitreous components may be elaborated from a single source. Such a hypothesis is in accordance with the view of Mann [7] that secondary vitreous is almost exclusively produced by the neural ectoderm.

The ratios of residual protein to vitreous weight in Column 6, Table, are lower than those previously mentioned. However, these data are not strictly comparable. The Friedenwald and Steihler value of 17 mg/100 cc. includes the zonular fibers, which were excluded in our work. The data of Bembridge, Crawford, and Pirie for the large, central portion of the vitreous shows 13 mg/100 cc. residual protein. This value is consistent with our determinations if it is assumed that their material was equilibrated with laboratory air.

The weights obtained from pooled samples are slightly higher than the averages of the individual weights. It is felt that the slight mechanical losses in the transfer procedures, being a greater percentage of the individual weights than of the pooled weights, account for this difference.

It is interesting to contrast the rate of eye development in cattle and in humans. According to the report of Wilmer,[8] the human eye nearly triples in weight from birth to adulthood. Whole body weight increases at the same time about twenty-fold. If we interpolate our bovine eye weights to time of birth, a weight of 13.5 gm. for the globe is obtained. Therefore, the bovine eye only doubles in size from birth to adulthood, while body size increases about thirtyfold.

Summary

Data are given for the weights of globe, vitreous, and residual protein of individual and pooled bovine eyes. Means for and variations in these weights are shown at four different age levels of cattle.

Residual protein is shown to increase at a rate parallel to growth of the vitreous during the period of growth of cattle. A highly significant statistical ratio of residual protein to vitreous weight is maintained throughout the entire period.

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The Effects of a New Drug, Nylidrin, upon the Electroretinogram

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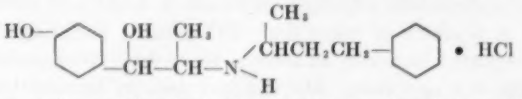
Henkes [1] originally demonstrated that vasodilator drugs can increase the amplitude of the b-wave of the electroretinogram. Upon the basis of this observation we studied the effects of several vasodilator drugs, as well as the effects of stellate ganglion block, upon the ERG. These results were published a short time ago.[2]

Recently, we undertook an analysis of the effects, upon the ERG, of a new drug, nylidrin hydrochloride (1-[*p*-hydroxyphenyl]-2-[1-methyl-3-phenylpropylamino] propanol hydrochloride) (Arlidin hydrochloride).

This drug is a synthetic, belonging to the epinephrine-ephedrine group of compounds,[3] and has a physiologically interesting triad of action. It increases the circulating blood volume *; it increases cardiac output,[4] and it also dilates the small vessels in skeletal muscle.† This latter action is thought to be due to relaxation of the smooth muscle fibers in the media of the small arteries and arterioles, and the drug is believed to act at the site of production of the so-called chemical transmitter substances.‡

The drug is rapidly absorbed from the gastrointestinal tract, absorption from this site being only slightly less rapid than after subcutaneous administration. Parenterally, activity is apparent within 3 to 7 minutes, and orally, within 7 to 10 minutes, whereas peak activity occurs within 15 to 20 minutes.[5] The doses we used, 12 mg. in a single oral dose, gave rise to no irritative phenomena.

The structural formula of nylidrin hydrochloride is



Our series consisted of 30 patients, varying in age from 20 to 61 years. The group was made up of 22 men and 8 women, and the eyes of these patients were essentially normal.

The subjects were each dark-adapted for 25 minutes, after which time a baseline ERG was recorded. In each instance, the patient was then given 12 mg.

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From the Division of Electrophysiology of the Research Department of the New York Eye and Ear Infirmary.

The Arlidin used in the study was supplied by the U. S. Vitamin Corporation. The study was supported by grants from the National Society for the Prevention of Blindness and the National Council to Combat Blindness.

* Ungar, G.: Personal communication to the authors, Jan. 29, 1956.

† Fulton, G. P.: Personal communication to the authors, February, 1956.

‡ Külz, F., and Schneider, M.: Personal communication to the authors, June, 1955.

of the drug, orally, after which ERG recordings were made at intervals up to 30 minutes following the administration.

The resulting b-wave was measured and its amplitude calculated as a percentage increase over the wave obtained before the drug was given. The results are presented in the accompanying Table and Graph. Our results showed that

Effect of Twelve Milligrams of Nylidrin Hydrochloride on Electroretinogram

Expressed as Percentages of Baseline ERG

Case No.	B-Wave Before Nylidrin Administration	B-Wave After Nylidrin Administration						
		3 Min.	5 Min.	10 Min.	15 Min.	20 Min.	25 Min.	30 Min.
1	100	100	133	135	160	150	167	160
2	100	100	120	150	150	166	150	146
3	100	106	106	119	119	119	123	119
4	100	105	112	118	125	125	120	120
5	100	121	121	148	157	148	148	160
6	100	100	111	119	122	122	122	111
7	100	108	110	115	125	125	120	110
8	100	100	100	120	140	140	140	130
9	100	114	122	122	122	131	131	123
10	100	114	131	131	131	122	122	114
11	100	125	125	143	162	162	143	125
12	100	125	125	162	187	187	187	143
13	100	108	114	122	131	131	131	122
14	100	108	122	122	131	131	122	122
15	100	106	116	116	126	123	133	117
16	100	106	120	120	126	133	133	117
17	100	100	116	133	123	116	116	116
18	100	100	114	128	128	114	114	100
19	100	100	106	116	111	113	113	106
20	100	100	106	116	119	116	116	106
21	100	100	100	108	114	114	120	108
22	100	100	108	108	114	120	114	108
23	100	100	102	108	114	114	108	102
24	100	100	106	116	133	133	126	116
25	100	100	102	111	120	128	125	116
26	100	100	102	111	120	128	125	116
27	100	100	106	111	111	122	106	102
28	100	100	106	111	122	122	111	100
29	100	100	111	116	116	125	125	111
30	100	100	111	118	118	124	124	111

the maximum effect of the drug upon the retina occurred between 15 and 20 minutes after oral administration. This time interval was in keeping with the findings of Riddell[6] in his studies of increased muscle blood-flow.

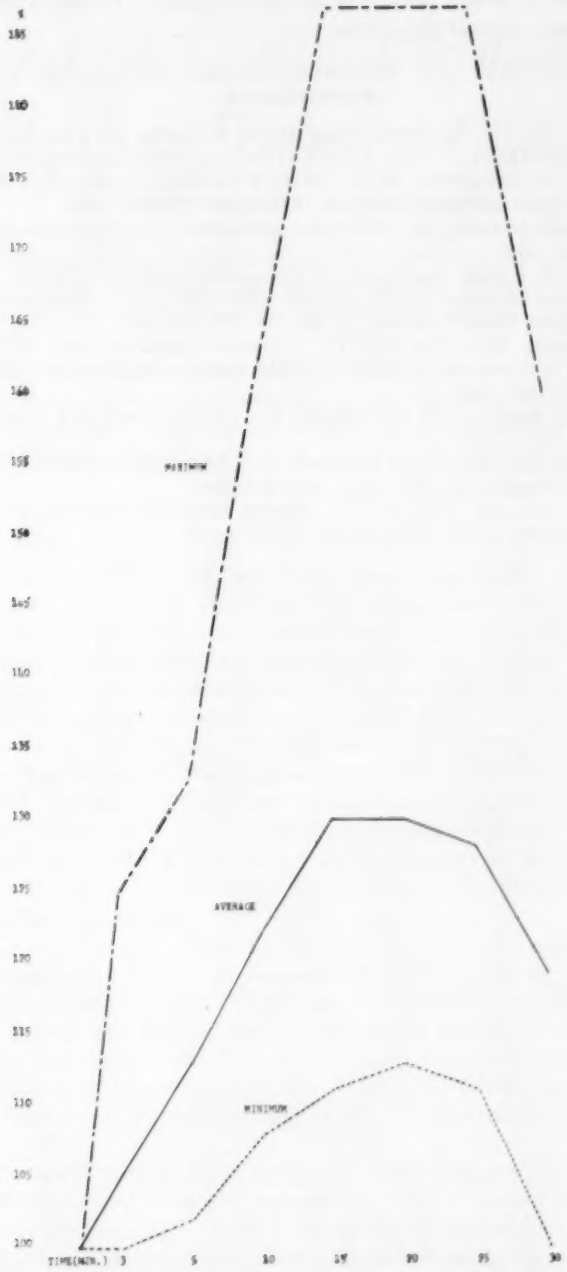
We found that the maximum b-wave increment averaged 32.9% above the baseline level and that there were no side-effects from the drug.

Hensel,[7] using the calorimetersonde, reported increases in blood-flow between 150% and 600%. Stein,[8] in a series of more than 200 patients suffering from occlusive arterial disease, reported increases in muscle blood-flow, after nylidrin, of 200% to 800% above the resting values. Marked increases in femoral blood-flow, in dogs, have also been reported after the administration of this new drug, and so our findings of a 32.9% increase in retinal blood-flow are of a similar order.

As stated in a previous paper,[2] it is not certain whether the increment in b-wave levels is due to increased blood-flow in the retina or choroid, or both. We have also employed nicotinic acid, stellate ganglion block, and papaverine and have shown that there is accord between the findings with use of this technique and the findings of others[9] using the nitrous oxide technique for measuring cerebral blood-flow.

Summary and Conclusion

A study of the effect of a new drug, nylidrin (Arlidin) hydrochloride, upon the b-wave of the electroretinogram was carried out in a series of 30 patients.



Graph of maximum, average, and minimum effect of 12 mg. of nylidrin hydrochloride upon the amplitude of the b-wave, expressed as per cent of baseline level.

Our results indicate that the drug is a potent vasodilator and produces an average increase in retinal blood-flow of just over 32%. It may be inferred that nylidrin increases cerebral blood-flow.

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Effect of Acetazoleamide on the Dark-Adaptation Function in Glaucoma

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It is well recognized that the light sense suffers in cases of chronic glaucoma.[12] Investigators as long as 30 years ago showed that the light minimum was considerably raised and the dark-adaptation rate retarded in cases of simple glaucoma.[11]

The carbonic anhydrase inhibitor acetazoleamide (Diamox) has recently found widespread acceptance among ophthalmologists as a new antiglaucoma agent. The purpose of this study is to determine whether the use of acetazoleamide has a detrimental effect on the dark-adapting function of the eye suffering from glaucoma.

Method and Material

The experiment consisted of periodically determining dark-adaptation curves of six glaucoma patients, all of whom were using pilocarpine therapeutically. Once a satisfactory "base line" curve was obtained, acetazoleamide administration was begun and was continued for varying periods of time and with varying dosages. The accompanying graphs are self-explanatory. It should be pointed out, however, that the points plotted under 0 weeks represent the base-line curve.

The subjects used in this investigation were the following:

CASE 1.—Age 80 years. The diagnosis of chronic simple glaucoma was made in April, 1954. At that time the patient had an intraocular tension of 32 mm. Hg (Schiøtz) OU and a positive water provocative test. Field examination reveals enlarged blind spots OU, a nasal step OD, and an arcuate defect OS. Vision at present is OD 20/30−2, OS 20/20 without correction. The patient uses pilocarpine 4% four times a day.

CASE 2.—Age 69 years. The patient was admitted to the Eye Service in June, 1954, with the diagnosis of glaucoma OU secondary to uveitis. The intraocular tension at that time was OD 43 mm. Hg (Schiøtz) and OS 53 mm. Hg (Schiøtz). During that hospital stay cyclodiathermy procedures were performed on both eyes. The patient has a large area of chorioretinitis involving the macular area of the left eye. Visual acuity is OD 20/20, OS 20/100, and the correction of small refractive errors gives no improvement. The patient uses 2% pilocarpine four times a day.

CASE 3.—Age 60 years. The diagnosis of chronic simple glaucoma was first made in March, 1952, when the tonometry readings were OD 40 mm. Hg (Schiøtz), OS 30 mm. Hg (Schiøtz). At that time the corrected visual acuity was OD 20/30, OS 20/30. The patient had an iridencleisis in the right eye in

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January, 1953. The patient now sees OD 16/200, OS 20/40 with correction. Pilocarpine 2% four times a day is used.

CASE 4.—Age 55 years. Diagnosis of glaucoma was made in June, 1950. At that time ocular tension was 34 mm. Hg (Schiøtz) in both eyes. Field changes include enlarged blind spots and baring of the blind spots OU. With correction the patient now sees OD 20/30−3, OS 20/20−1. The patient uses pilocarpine 2% four times a day.

CASE 5.—Age 42 years. This is the only female patient in the series. The diagnosis is chronic simple glaucoma. The patient was first seen at the Eye Clinic in March, 1952, seeing OD finger counting at one foot, OS 20/50. The tonometry reading at that time was OD 59 mm. Hg (Schiøtz), OS 40 mm. Hg (Schiøtz). Iridencleisis was performed on the left eye in April, 1954. The field of the left eye is about 15 degrees with a 1/1000 white test object, 25 degrees with a 3/1000 white test object. The patient is using pilocarpine 2% four times a day. The present visual acuity is OD no light perception, OS 20/40.

CASE 6.—Age 60 years. This patient has been known to the Eye Clinic since March, 1949, as having a case of chronic simple glaucoma. Tonometry readings at that time were 31 mm. Hg (Schiøtz) OU. Field changes include baring of the blind spot OD. At present the corrected vision is OD 20/40+4, OS 20/15. The patient is using pilocarpine 4% four times a day.

The dark adaptation data were obtained in the following manner.

Apparatus: A Goldman-Weekers self-recording dark adaptometer was used, which is an automatically recording adaptometer permitting direct logarithmic records.

The light adaptation mechanism is a concave bowl which causes uniform light adaptation of the observer over a large part of the retina when the observer's head is placed in proper relationship to the bowl. The intensity illumination can be read with a built-in photoelectric meter. The arrangement for measuring dark adaptation consists of:

(*a*) A source of light. A current-smoothing device maintains a steady light independent of fluctuations in the main supply. The general level of illumination of the test object can be altered by a variable shutter according to a built-in photoelectric light meter.

(*b*) A neutral gray wedge filter permits moment to moment reduction of the illumination of the test object—down to 1/10,000,000 of the basic illumination. The gray wedge is linked to a recording device, traveling over a logarithmic chart, on which it shows the setting of the wedge. The brightness may be repeatedly recorded on the chart as often as required by pulling the control knob for the gray wedge. The recording drum turns at the rate of 4.5 mm/minute.

(*c*) Field size. The test plate is an opal glass 56 mm. in diameter, which is equal to 11 degrees at the examining distance of 30 cm. Opaque black stripes are on the test plate (test plate 39/I). If the patient can tell in which direction the stripes be, the patient is considered to have been dark-adapted as far as that particular light intensity level is concerned.

(*d*) The fixation is on a light from a red bulb, the strength of which may be varied at will by the examiner. The fixation point is 11 degrees above the center of the test plate.

(*e*) Calibration. The test field has a maximum strength of 9 lux. The adapting field has the strength of 1700 lux.

Procedure: The subject first remains in a moderately illuminated room for 15 minutes. Then the subject stays in a completely dark room for five minutes, following which he is light adapted at 1700 lux for seven minutes. The initial brightness for the exciting field is 9 lux. Test plate 39/I having a striped figure with 100% contrast is used.

As soon as the subject proves his ability to see at the initial test plate level, this level is recorded. The intensity of the test plate stimulus is then reduced until it is below the patient's threshold of that moment. As soon as the patient is again able to identify the target, this new level is recorded, etc. The patient's dark adaptability is tested over a period of 30 minutes in each case. The test is conducted on a monocular basis; the same eye is always used in a particular subject.

Findings

The experimental results are presented in graph form. In these graphs the absolute threshold of perception in log units is plotted against duration of acetazoleamide therapy in weeks. Points representing the same duration of dark adaptation in the different experimental sessions are joined with a line. The plots on the 0 week line represent the performance of the subject before any acetazoleamide administration. In all subsequent experimental periods the subject is performing under whatever influence acetazoleamide had. The specific dosages involved are evident from inspection of the graphs. The number in parentheses under the various plots represents the tonometry reading of the examined eye on that particular occasion.

In all cases except one (Case 4), the last 30-minute threshold value obtained (under the influence of acetazoleamide) is lower than the 30-minute level existing

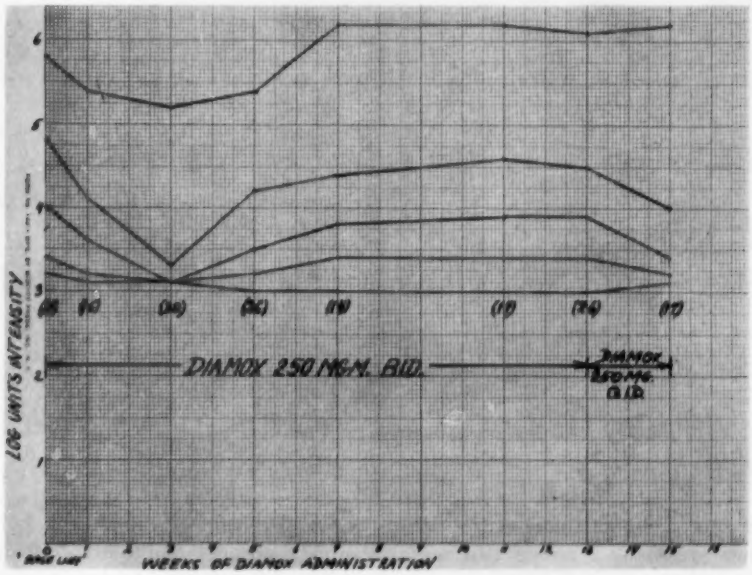

Fig. 1 (Case 1).—Left eye, vision 20/20. The curves on the graph, reading from top to bottom, represent dark adaptation at 0 minutes, 5 minutes, 10 minutes, 15 minutes, and 30 minutes.

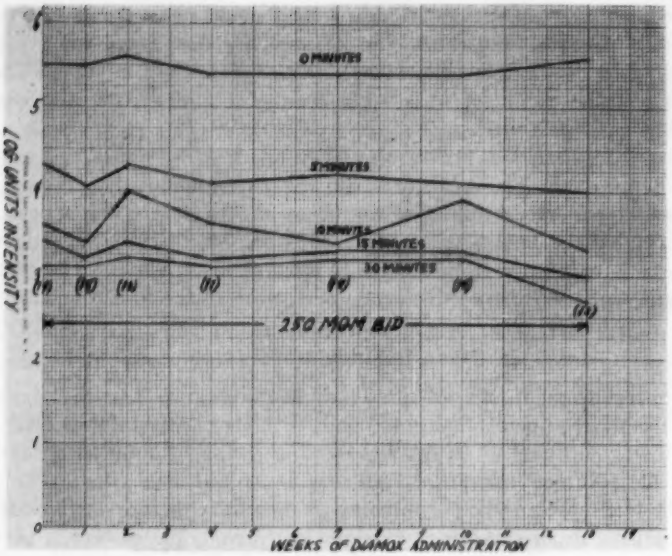

Fig. 2 (Case 2).—Right eye, vision 20/20.

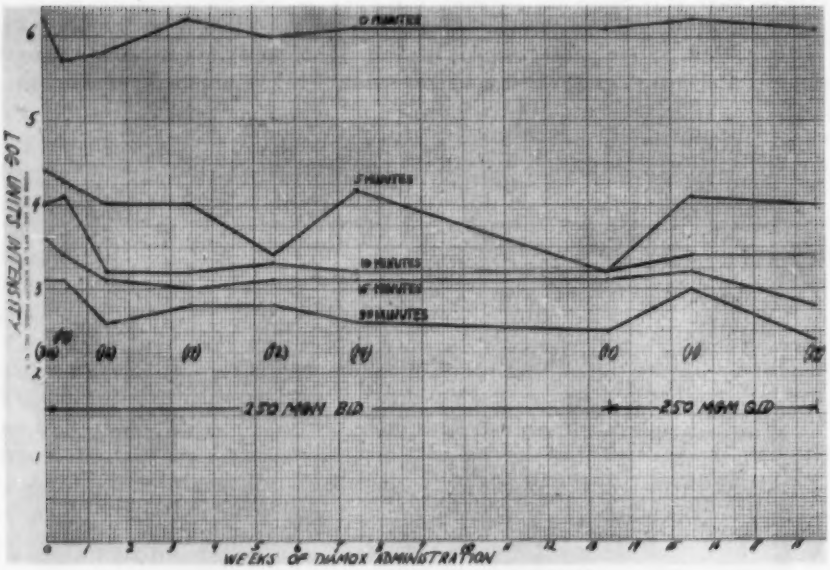

Fig. 3 (Case 3).—Left eye, vision 20/30.

before acetazoleamide administration was begun. Probably this finding should not be interpreted as meaning that acetazoleamide improves ability to dark-adapt. It most likely signifies that with experience the subject becomes more able in the test situation. To obviate this factor three practice runs are made with each subject before experimental data are taken, but in all likelihood this measure is not

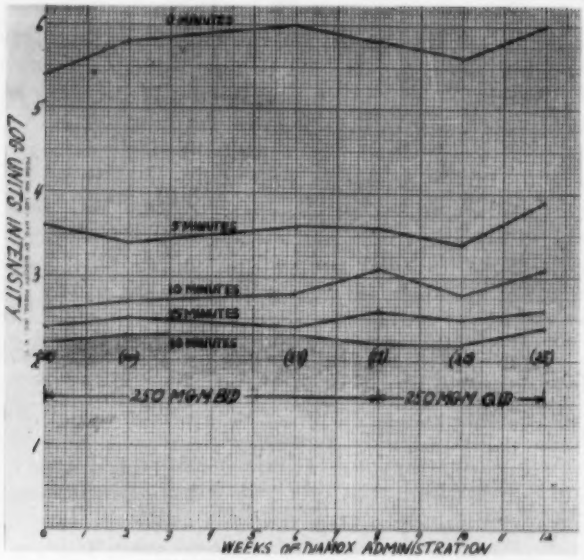

Fig. 4 (Case 4).—Left eye, vision 20/20.

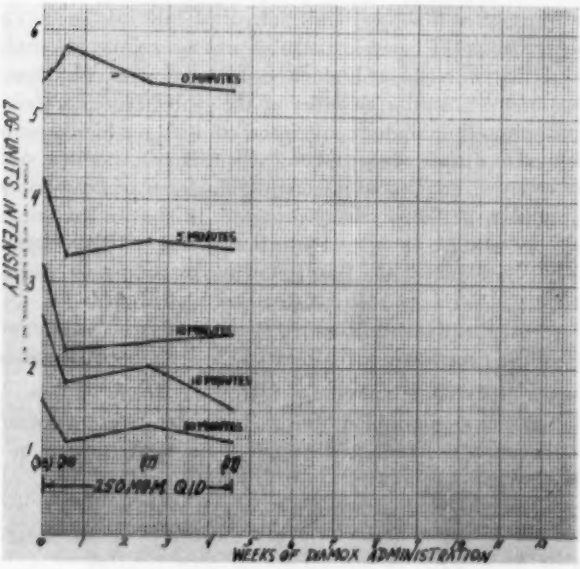

Fig. 5 (Case 5).—Left eye, vision 20/50.

totally effective. A similar finding occurs at the 5-, 10-, and 15-minute levels of dark adaptation.

Comment

Theoretically, acetazoleamide might have a detrimental effect on the dark-adapting function of the eye. This can be understood from a consideration of the action of acetazoleamide and the nature of dark adaptation. The first clinical

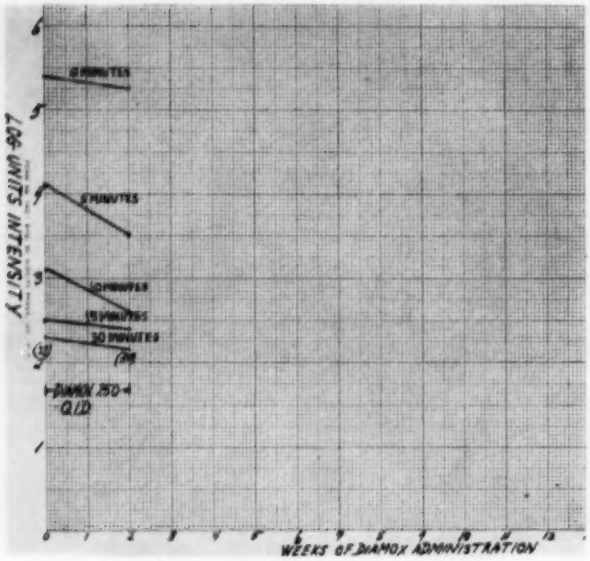

Fig. 6 (Case 6).—Left eye, vision 20/15.

investigators * suspected that a carbonic anhydrase inhibitor such as acetazoleamide would be able to control elevated intraocular pressures from the study of Kinsey,[15] which revealed that a remarkably high concentration of bicarbonate ion exists in the aqueous of the posterior chamber of the rabbit eye. The possibility existed that a carbonic anhyrase inhibitor could interfere with the high aqueous bicarbonate level. Other evidence that suggested that the ciliary processes secreted aqueous aided by the catalytic activity of carbonic anhydrase was contributed by Westrand.[20] He found in perfused ciliary processes of the iris of the rabbit carbonic anhydrase activity as high as one-seventh that found in the animal's erythrocytes.

Friedenwald [13] postulated that the following reaction took place in the ciliary processes:

$$O^- + H_2O \longrightarrow 2\ OH^- + CO_2 \longrightarrow HCO_3^- \quad H_2O \quad Na \longrightarrow$$

cytochrome system carbonic anhydrase → to posterior chamber

The presence of carbonic anhydrase favors movement of the equation to the right. When acetazoleamide inhibits the carbonic anhydrase present in the ciliary processes, the equation proceeds to the right at the much slower uncatalyzed rate; less HCO_3 is secreted, less aqueous is produced.

The enzyme carbonic anhydrase is present in relatively high concentration in other parts of the visual system. Whether the use of acetazoleamide can affect the function of these parts is an interesting consideration. Specific sites mentioned in the literature because of their high enzyme content have included the lens [4] and the retina.[14]

There is evidence of much carbonic anhydrase activity in the central nervous system, of which the visual pathways are a part. This is particularly noteworthy since it has been shown, as will be re-emphasized later, that dark adaptation may be a function, at least in part, of the central nervous system.[16] Ashby † found

* References 5 and 6.

† References 1 and 2.

that the carbonic anhydrase activity of the central nervous system is 7% to 14%, that of the animal's blood, and believed that the enzyme functions in the chemical activity of the nervous tissue itself and is not simply concerned with the elimination of the metabolic end-product CO_2. This investigator thought that perhaps the enzyme plays a part in determining the speed with which energy is made available for nerve impulse conduction.

Davenport,‡ like Ashby, noted the relatively high levels of carbonic anhydrase activity in nervous tissue but found that, in experiments with cat peripheral nerve, cat spinal cord, and rabbit cortex, function did not seem to be inhibited by amounts of carbonic anhydrase inhibitor that diminished the enzyme activity by 99.9%. He warned that some biochemists were assigning undue importance to certain enzymes, particularly carbonic anhydrase, merely because they were found in high concentration in various tissues. He stressed the following points:

1. An enzyme only speeds the rate at which a reaction attains equilibrium and has no effect on the equilibrium.

2. Whether an enzyme actually catalyzes a reaction depends upon the presence and concentration of its substrate as well as on the presence of the enzyme.

3. The concentration of an enzyme in a particular cell or part of a cell is not evidence for the relative importance of the reaction the enzyme catalyzes.

4. The amount that a catalyzed reaction is reduced by inhibition or destruction of an enzyme is not necessarily proportional to the degree of inhibition or destruction of the enzyme.

Since carbonic anhydrase occurs in significant quantities in the eye and the central nervous system, and since there is much evidence that dark adaptation is the function of the many portions of the visual apparatus, from retina to visual cortex, the possibility exists that the enzyme carbonic anhydrase plays an important role in the dark-adaptation mechanism. Acetazoleamide may deleteriously affect the process through carbonic anhydrase inhibition.

The idea that dark adaptation is the reflection of the activities of the retina and the various parts of the central nervous system was not held in the past, nor is it universally accepted at present. Perhaps the best-known theory of dark adaptation is the photochemical one, which holds that the ability to see with reduced illumination is related to the amount of unbleached visual purple in the rods of the retina. According to this concept, the major if not the sole site for dark-adaptation processes is the retina.

Although this theory explains some of the experimental findings, it has many flaws. Lythgoe [17] discussed these shortcomings in detail and proposed a new concept of dark adaptation. He offered the idea that adaptation results from the rearrangement of synaptic connections, presumably in the retina.

There has been experimental support for this view. Arden and Weale [3] found in their experiments that as dark adaptation proceeds the integrating power of the retina increases, probably owing to the rearrangement of the neural elements. Their data seem to indicate that the greater dark adaptability of the extrafoveal regions as compared with the foveal area is due to spacial summation, resulting from the greater number of interconnections between percipient elements in these extrafoveal regions.

Crozier,§ using a different experimental approach, has concluded that the

‡ References 9 and 10.

§ References 7 and 8.

dark-adaptation curve can be explained not on the basis of photochemical reaction but in terms of the number of neurons available at any given time within the entire visual pathway. Krieger and Bender,[16] while studying dark adaptation in perimetrically blind fields, concluded that the phenomenon takes place at least in part in the central nervous system. Another group of workers[19] showed that breathing an atmosphere containing 32% to 36% oxygen causes the visual threshold to fall approximately to one-half the normal value within 5 to 10 minutes. This alteration in threshold can be abolished and even reversed by adding carbon dioxide to the inspired air mixtures. It would seem that the creation of a relative alkalosis or acidosis in the brain's environment has a marked effect on dark adaptation.

The experimental thesis may be summed up as follows:

1. Dark adaptation is a function of the retina, its nervous connections, and the central nervous system.

2. Carbonic anhydrase occurs in relatively high concentration in the retina and in nervous tissue, including the central nervous system.

3. The possibility exists that the administration of acetazoleamide, a carbonic anhydrase inhibitor, may embarrass the function of the retina and the rest of the visual system, which may be reflected in a decreased ability to dark-adapt.

4. The subjects used all have glaucoma. This selection was deliberate and was done for two reasons: (*a*) Glaucoma patients are exposed to intensive acetazoleamide therapy. (*b*) If the function of dark adaptation is vulnerable to the effects of acetazoleamide, glaucoma patients may demonstrate this the best, for in them the function may be already compromised.

Conclusions

The sum of the experimental data would indicate that acetazoleamide given in divided dosages of 0.5 or 1 gm. a day does not adversely affect the dark-adaptation function in the patient suffering from glaucoma.

Some possible explanations for this finding are the following:

1. The reserve of carbonic anhydrase in the retina or central nervous system is not reduced or not reduced sufficiently by the dosage of carbonic anhydrase inhibitor used.

2. Uncatalyzed reactions are sufficient to maintain the integrity of the function studied.

3. Carbonic anhydrase plays no part in the function of dark adaptation.

Dr. Goodwin M. Breinin suggested the subject for this paper and aided in the study.

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Stereopsis and Unequal Luminosities of the Images in the Two Eyes

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Introduction

The extent to which a difference in the luminosities of the images in the two eyes can affect binocular vision and, in particular, stereoscopic depth perception has been an intriguing problem to research workers in vision for a long time.

The most striking effect, of course, is the Pulfrich stereophenomenon, in which the stimulus object is in motion relative to a fixed background. The bob of a swinging pendulum appears to move in a more or less elliptical path when the image of one eye is darkened by a filter. This phenomenon is usually explained by a decreased reaction time in the physiologic processes of one eye associated with the decreased intensity of its image. The second effect, which may be called "irradiation stereoscopy,"[1] was first discovered by Münster[2] in 1941 and later independently by Cibis and Haber.* In this effect, two separated squares of white cardboard, both in the frontoparallel plane on either side of a fixation point, will appear to have been rotated through a small angle equally and in the same direction about vertical axes (a Venetian-blind effect) when the image of one eye is darkened by a filter. The effect is due to the fact that the phenomenon of "irradiation" causes a shift in the positions of the perceived contours of the retinal images of the squares, and the effective size of the square is thus made to appear smaller to the darkened eye. The apparently rotated position of the square is explained, then, on a geometric basis, just as is explained the apparent rotated position of objects about a vertical axis when the image in one eye is magnified horizontally by an afocal meridional magnifying lens.[5]

That an effect on the stereoscopic depth occurs with ordinary and static spatial configurations has been less certain. Verhoeff[6] (1933) described his observations with a stereoscope in which he used equally inclined black lines on a white background as test targets (Fig. 1) and then darkened the image in one eye by a smoked glass or filter. When the absorption of the glass was of the order of 80% to 95%, depending on background illuminance (and the luminosity of the background was regarded as that of the image), he reported two effects: (1) The fused image appeared to deviate laterally toward the brighter image, and (2) the stereoscopic sagittal inclination of the line was reduced about

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* References 3 and 4.

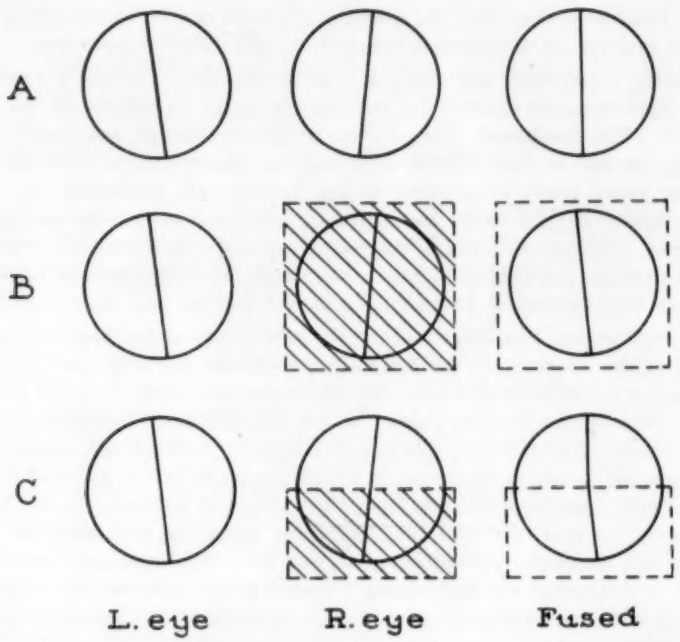

Fig. 1.—Type of target patterns used by Verhoeff in a stereoscope, and the apparent figure experienced binocularly, except that the sagittal (fore-and-aft) stereoscopic inclination of the line cannot be illustrated.

one-third. "The effect on the apparent position of the [line] as regards lateral displacement and depth is the same as would result from a displacement [of the darker image] toward [the brighter image] when their luminosities were equal."[7] This lateral deviation, which Verhoeff stated is proportional to the difference in the luminosities, and to the disparity, "has the effect of reducing the disparateness"—and therefore the stereoscopic depth. Verhoeff concluded: "The phenomenon occurs with any kind of disparate images."[6]

The generality implied in this last-quoted sentence is hardly justified on the basis of the introspective observations. Nevertheless, it has been accepted. In referring to Verhoeff's observations, Miles[8] wrote: "Reduction in illuminance in one eye causes proportional [sic] loss of stereoscopic acuity," an effect which, in his opinion, is somehow related to a rivalry phenomenon from unequally illuminated images. Verhoeff, of course, discussed only a decrease of stereoscopic depth and not stereoscopic acuity.

On the other side of the picture, Schaefer and Ebner[9] reported an enhancement of stereoscopic depth and an improvement in stereoscopic acuity from placing a colored filter before one eye. Similarly, Engel and Fischer[10] implied that an illumination difference of the two eyes is capable of extending the area of our depth perception to much greater distances than was previously anticipated according to the laws of stereoscopy. Charnwood,[11] however, stated that he could not find these effects. The possibility that unilateral darkening of the images of one eye may lead to a subjective enhancement of depth, even beyond the stereoscopic limiting distance, was also suggested by Trincker,[12] especially in relation to the Pulfrich stereophenomenon and to the role played by eye move-

ments. Thus it is clear that the possible effect of unilateral darkening of the image of one eye on stereoscopic vision is by no means unequivocal.

Recently Dyckerhoff and Siebeck [13] have repeated Verhoeff's experiment, using a haploscope to observe the stereoscopic image of figures on the targets drawn on white cardboard. The mirrors of the haploscope were only partially reflecting, so that in front of the apparatus the experimenters were able to set up a line which could be adjusted to any fore-and-aft inclination and thus be made to appear parallel to the inclination of the fused stereoscopic image of the target lines. Their results, which, they stated, agreed with Verhoeff's observations in many respects, are difficult to assess, because of some fundamental error which must have been present in their analysis, as will become clear later in this paper.

The experiments just described and the conclusions stated have an important bearing on the problem of the relationship between disparity and stereoscopic depth and on the problem of the stability of stereoscopic depth for given disparities between the images. The implication is that the difference in luminosity of the images results in a decreased physiologic disparity between the images. Now, there are many instances, of course, in which empirical factors will tend to reduce and even mask stereoscopic depth from given disparity patterns. In the Verhoeff experiment, however, no additional empirical factor is introduced by simply changing the luminosity of the image in one eye. With configurations such as he used, cyclofusional eye movements [14] would be a factor in the actual depth perceived, but these movements cannot themselves explain a reduction in stereoscopic depth.

The results of three experiments to test the basic phenomenon will be reported in this paper. It can be stated at the outset that the statement of Verhoeff to the effect that the phenomenon occurs generally is not confirmed. There appears to be a stability in the stereoscopic depth from disparate images for wide differences in luminance of the image of one eye compared with that of the other as long as both images are perceived.

I

The basic experiment was to determine the validity of stereoscopic perception of depth, and the stereoscopic acuity from the disparate images of a single stimulus, when a filter is placed before one eye or before the other so as to reduce the luminosity of one of the disparate half-images.

Apparatus.—The instrument used was a further modification of the haploscopic device previously described.† Figure 2 is a schematic drawing of the apparatus. The subject's head was carefully adjusted to the instrument, so that the eyes would be level and centered with respect to the axes of the instrument, and was held in position by a sturdy head rest and a wax bite or chin cup. The subject fixated with symmetrical convergence a brightly illuminated spot (1 mm. diameter) on a thin sheet of plate glass 50 cm. from the eyes. The subject also saw the images of both a reference and a test object by reflection from suitable mirrors (50-50 transmission-reflection). Secondary reflections from the back surfaces of the mirrors were reduced by coating. The reference object consisted of a thin polished steel drill rod, mounted vertically and seen by reflection from a fixed mirror. The position of the rod could be adjusted so that when seen stereo-

† References 15-20.

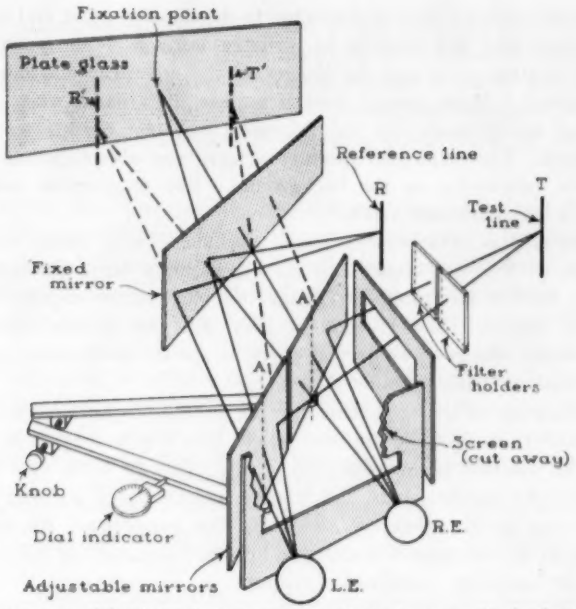

Fig. 2.—Instrument of haploscopic type used to study stereoscopic depth perception, with which the effect of darkening the image of the test object seen by one eye could be measured.

scopically it could be located at any position before or behind the fixation point and could be set at any desired peripheral angle. This rod, when suitably illuminated, produced a brilliant vertical bright line.

The test object was also a drill rod, identical to that used for the reference object, and was seen by reflection from the double-mirror combination nearest the eyes. These two mirrors, when turned about vertical axes (*A-A*) through small angles in directions opposite to each other, produced a change in the disparity between the images of the test object and, accordingly, a change in the stereoscopic depth of the test object relative to the fixation point or to the reference line. The mirror rotations were controlled by a handwheel through suitable levers and a screw. The angle of disparity was always symmetrical about a given lateral position of the test object. The reference and test stereoscopic images were placed on either side of the fixation point at extrafoveal angles of 1 arc degree. When the operator turned the handwheel controlling the rotation of the mirrors, he thereby changed the angular disparity of the images of the test line with respect to the fixation point and the reference line, and the test line appeared to move stereoscopically nearer or farther. A dial indicator, which showed the amount the mirrors had been turned, and therefore the angular disparity of the images of the test line, was calibrated in minutes of arc. An estimated one-fifth scale division corresponded to 6 seconds of arc angular disparity.

The reference and test rods were illuminated by lamps on the same electric circuit. By means of a time switch inserted in the circuit, the two could be illuminated momentarily for 0.2 second when a push-button switch was used by the experimenter. This exposure was short enough to prevent the influence of eye movements and at the same time was long enough to assure an adequate stimulus for stereoscopic depth perception.

The binocular visual field was restricted to the fixation point and to the images of the reference and test objects by suitable horizontal slit apertures and a septum. The fixation point and the images of the reference and the test objects were seen against a large, evenly though weakly illuminated white background. The individual backgrounds for the reference and test objects were, however, completely black. The principal aperture screen was also illuminated so as to have the same brightness as the background. The experiment was otherwise conducted in a semidarkened room.

This experimental arrangement made possible a wide range of disparities of the images of the test object and correspondingly large changes in stereoscopic depth. Within this range the images did not change angular size, brightness, or their optical distance, that is, they did not become blurred as the stereoscopic depth changed. Empirical clues to spatial localization from the test object were thus virtually eliminated.

The modification of the apparatus for the present experiment was the interposition of holders in front of the test object into which 2 by 2 in. neutral-tint filters could be inserted before one eye or the other or both. By using filters with different light transmissions, the relative luminosity of the test object could be varied for one or the other eye. Thus, in this experiment, the luminosity of the test object to the two eyes was changed but the luminosity of the fixation point and of the surroundings remained constant.

Procedure.—Three subjects were used in this study. All had had experience in stereoscopic observations. In the experiment the first subject used a +1.25 D. sphere before each eye to correct for partial presbyopia and to eliminate a small esophoria. Although the second subject was about 0.50 D. myopic in each eye, no glasses were used in the experiment. The third subject wore spectacles to correct an astigmatism.

Data were taken to determine (1) the disparity corresponding to the most probable position of the test line when it and the reference line appeared equally distant and (2) the stereoscopic acuity, as neutral-tint filters of different light transmissions were inserted to change the luminosity of the image of the test line for one eye. Since the Verhoeff phenomenon was said to occur only when there was a disparity between the images of the test object, data were obtained when the reference line was placed in front of (or behind) the plane of the fixation point, for in this position the images of the reference line would then be disparate. If the test line was then set so as to appear the same distance, its images would correspondingly be disparate. One must keep in mind that only the disparate images of the test line and not the fixation point or reference line are affected by the filters.

The psychophysical method of constant stimuli, of the forced-choice, two-category type, was used in this part of the study. In a given set of observations, 100 exposures of the test images, in a range of five equally separated disparity settings, were presented to the subject in random order—random except that in each five presentations all five of the disparities would have been used. The subject held a rigid fixation on the fixation spot. Immediately after the exposure, the subject was asked to indicate whether the test line had appeared "nearer" or "farther" than the reference line. If uncertain, the subject was forced to guess. When the percentage of times the test line appeared nearer (or farther), for each disparity category, is plotted graphically, one obtains the usual psychometric curve.

From such data can be computed ‡ (1) that disparity, η_o, in minutes of arc corresponding to the 50-50 level on the curve and (2) the standard deviation, S, in minutes of arc. The first corresponds to the most probable disparity for the apparently "equal" distance, and the second is related to the slope of the curve, is proportional to the threshold of stereopsis, and is inversely proportional to the stereoscopic acuity.

Results.—The procedure was then to obtain values of η_o and S for a series of different absorption filters before one eye or the other, for several different positions of the reference line nearer or farther than the fixation point. The extent to which the disparity, η_o, changes with unequal luminances of the images of the two eyes shows the extent to which stereoscopic depth was altered by those differences in luminosities. The variation measured by S shows the extent to which the threshold of stereoscopic perception of depth similarly varies. The results for two subjects are summarized in Table 1. In the left column are given

TABLE 1.—*Effect of Reducing the Luminosity of the Image of One Eye on Stereoscopic Depth Perception* *

Reference Position	Subject 1					Subject 2				
	Filter	η_o	S	$\Delta\eta_o$	V	Filter	η_o	S	$\Delta\eta_o$	V
7.5 mm. nearer	None	6.55	1.16			None	5.21†	0.49†		
	10% R	6.75	1.09	+0.20	+2.2	5% R	4.22†	0.49†	−0.99	+1.7
	10% L	5.93	1.11	−0.62		5% L	5.53†	0.53†	+0.32	
5 mm. nearer	None	4.74	0.67			None	3.55	0.52		
	10% R	5.23	1.01	+0.49	+1.6	5% R	4.01	0.37	+0.46	+1.1
	10% L	4.67	0.65	−0.07		5% L	1.96	0.47	−1.59	
On plane	None	0.58	0.91			None	0.00	0.31		
	10% R	0.52	0.70	−0.06	None	5% R	1.15	0.40	+1.15	None
	10% L	0.16	0.87	−0.42		5% L	−0.26	0.43	−0.26	
5 mm. farther	None	−2.92	1.30			None	−3.03	0.59		
	10% R	−2.94	0.67	−0.02	−1.0	5% R	−3.06	0.49	−0.02	−1.0
	10% L	−3.62	0.79	−0.70		5% L	−3.47	0.54	−0.44	
7.5 mm. farther	None	−5.90	0.95			None	−4.83	0.45		
	10% R	−4.75	1.55	+1.15	−2.0	5% R	−3.75	0.76	+1.08	−1.6
	10% L	−8.14(?)	1.41	−2.24		5% L	−4.62	0.50	+0.21	

*Measured most probable disparity, η_o; standard deviation, S; change in disparity, $\Delta\eta_o$, associated with the use of filters; V, change in disparity predicted on basis of Verhoeff's observations. Data in minutes of arc (values given) have been corrected for magnifying effect of the filter glass.
†Average of five independent sets of data.

the positions of the reference line, nearer or farther than the fixation point for the two subjects. These distances were not precisely set, but they did remain constant throughout the measurements for each subject. Hence, the disparity η_o when no filters were used may not be the same for different subjects, apart from the effect of differences in interpupillary distances. For each subject the next five columns give (1) the filters used, with the per cent transmission; (2) the measured disparity, η_o; (3) the standard deviation; (4) the difference in the disparities, $\Delta\ \eta_o$, that might be attributed to the effect of the filters, and (5) the

‡ The method outlined by J. Berkson (Estimate of the Integrated Normal Curve by Minimum Normit Chi-Square with Particular Reference to Bio-Assay, *J. Am. Statist. A.* 50:529-549 [June] 1955) was used for this calculation.

magnitude of this difference that might be expected on the basis of Verhoeff's observations. Only the data for the 10% and the 5% transmission filters before the test object seen by one eye or the other are shown, since it was only in this range of luminosity difference that the Verhoeff effect was said to be found.

It will be clear from an inspection of this Table that the disparity obtained with a filter before one eye or the other is not significantly different from the disparity obtained with no filters, regardless of the position of the reference line. If the general statement of Verhoeff were valid, the measured disparities, corresponding to equal depth with respect to the reference object, should be greater, since the reference object was unaffected by the filters, if the subjective depth corresponding to a given disparity were decreased by the difference in luminosity. Furthermore, there is no consistent trend. One should also note that there is no significant difference or trend in the thresholds (S) of stereoscopic depth, that is, of stereoscopic acuity. One must conclude that the subjective stereoscopic depth from isolated test stimuli is little influenced by decreasing the luminosity of one of the disparate images. It would be incorrect to say that the filters have no effect on stereopsis, for obviously with such experimental conditions the visual processes are called on to associate a fainter, narrower image seen by one eye with a more luminous and wider image seen by the other eye. In general, it is the images of contours that provide the stimulus for stereoscopic depth. Which contours in this situation are selected and how stable this selection is could be a source of considerable variation in the results.

In order to eliminate the possibility that the equating of subjective depth of the test line with that of the reference line could be made by clues other than the stereoscopic response, such as equating disparities, the experiment was modified so that, with the reference line set 7.5 mm. nearer than the fixation point, the subject was asked to judge when the test line appeared to be as far behind the fixation point as the reference line appeared in front. Table 2 shows the results for two subjects. The columns have the same designations as those in Table 1. Under this experimental condition, if the disparity of images is reduced by virtue of the unequal illumination of nearly a third (Verhoeff), one would expect the difference in the disparity between "with filter" and "no filter"

TABLE 2.—*Validity of Stereoscopic Depth*

Filter	Subject 1			Subject 2		
	η_0	S	$\Delta\eta_0$	η_0	S	$\Delta\eta_0$
None	−5.90	1.88	.....	−5.60	2.86	.....
10% R	−4.91	1.41	+0.99	−5.00	2.18	+0.60
10% L	−5.70	1.51	+0.20	−4.82	4.14	+0.78
10% R 50% L	−4.51	1.46	+1.39	−4.71	2.60	+0.89
50% R 10% L	−4.49	1.57	+1.41	−4.82	2.23	+0.78

*The measured disparity, η_0, corresponding to the position of a test needle when it appeared stereoscopically as far behind a fixation point as did a reference needle 7.5 mm. in front of the plane of the fixation point; the standard deviation, S, of the distribution, and the difference in disparity, $\Delta\eta_0$, attributable to the effect of the filters. Data are given in minutes of arc.

to be about −2.0 minutes of arc. That is to say, a larger disparity would have had to be introduced between the images of the test line if it were to appear as far behind the plane of the fixation point as the reference needle (whose images were uninfluenced by the filters) appears in front of that plane. Inspection of the Table shows a tendency for the deviation actually to be in the opposite direction.

It must be concluded from these fundamental experiments that a difference in the luminosities of disparate images themselves in the two eyes does not result in a decreased stereoscopic depth. As long as the contours of the test object are perceptible, the stereoscopic depth is essentially the same.

II

The next step was to study the apparent inclination of a line, as in the experiment of Verhoeff. In order to avoid the use of the drawn figures to be observed in a stereoscope, an actual stimulus line was set up so that it could be inclined sagittally (fore-and-aft) in the median plane. The degree of apparent inclination could also be measured by a second test line.

Apparatus.—Figure 3 illustrates schematically the apparatus used. A subject, whose head was held rigidly in a suitable head rest and chin cup, observed in

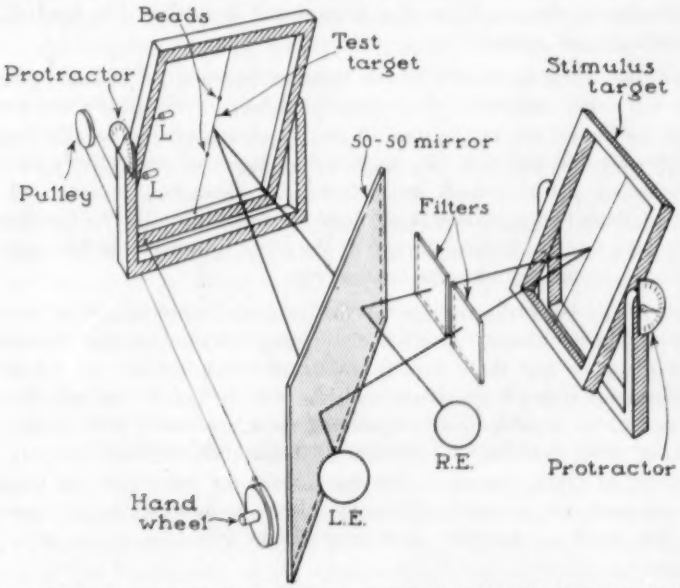

Fig. 3.—Sketch of experimental set-up used to test the effect of darkening the image of one eye on the apparent stereoscopic inclination of an inclined line.

symmetrical convergence a test stimulus line at a distance of 50 cm. by reflection from a fixed 50% transmission—50% reflection mirror, and also observed through the mirror a test line at the same distance in front. The stimulus line was a tautly stretched heavy white thread mounted in a frame, which could be turned about a horizontal axis and set at any degree of inclination, and thus seen inclined sagittally in the median plane by the subject. Suitable apertures prevented the

subject from seeing the supports for the thread. This thread was illuminated by a lamp attached to the frame, an arrangement which maintained constant illumination of the thread, regardless of inclination. The background was a black velvet cloth. Between the mirror and the stimulus thread, neutral-tint filters could be so placed that the intensity of the image of the stimulus line could be decreased for either eye.

Out in front of the mirror, the test device was also set up in a frame that could be turned about a horizontal axis by which one could obtain any desired sagittal inclination of the frame. The test device consisted of two small white beads strung on a taut black silk thread, attached at the top and bottom of the frame through the center. These beads were illuminated by separate small projection lamps attached to the frame. Again, apertures and a septum restricted the visual field to the beads, which were also seen against a black background. The thread supporting the beads was invisible against the black background. The inclination of the line of the test beads could be adjusted by the subject by means of a hand wheel. The angle of inclination of the frame was read from a protractor and pointer by the operator. The experiment was conducted in a totally dark room. The mirror was so adjusted that the beads would appear to the side of the illuminated stimulus thread about ½ arc degree. An interrupter-timing device was inserted in the electric circuit for the projection lamps which illuminated the beads, so that they would be visible for one-half second, at intervals of one second.

Procedure.—The inclination of the stimulus line was set at some given angle, with the top either toward or away from the subject. The subject was then asked to adjust the line of the two beads (1) so that they appeared parallel (sagittally) to the stimulus line and then (2) so that they appeared subjectively vertical also in the sense of a fore-and-aft inclination. The average of a series of settings for each of these two criteria was obtained as neutral-tint filters of various transmissions were inserted before one eye or the other to reduce the luminance of the retinal image of the stimulus line in that eye.

Now, it has been shown that in the binocular observation of a sagittally inclined line, in the absence of other dominating contours in the binocular visual field, there can be and there usually are small cyclotorsional movements of the eyes, movements that are consistent with the role of fusion—to keep the dioptric images as near as possible on corresponding retinal points.[13] It is usually difficult not to have some cyclofusional movements from such inclined contours even in the presence of other contours. For this reason the test device as used in this experiment must not of itself additionally initiate or influence cyclofusional movements. The bead arrangement with intermittent exposure serves as a suitable test device.

When a stimulus line is inclined sagittally in the median plane from the vertical, each of the retinal images deviates in a rotary sense in opposite directions about the axes of fixation. The total angular deviation (about the axes of fixation) of the two images from the vertical is designated a "declination," δ_s.[13] The angle of inclination (i_s) of the stimulus line in the median plane, measured from the vertical, is related to the geometric angle of declination, δ_s, by

$$\tan \delta_s = 2a \tan i_s/b,$$

in which $2a$ is the interpupillary distance and b is the observation distance

measured from the interpupillary base line.§ The line appears inclined in space because of the stereoscopic responses to the horizontal disparities between the images in the two eyes of all parts of the line.

It is also the declination between these images that provides the stimulus for cyclofusional movements of the eyes. The actual inclination, i_τ, of the test beads when they are adjusted so that they appear vertical is related to the total angular cyclotorsion, τ, of the two eyes by the same formula, namely

$$\tan \tau = 2a \tan i_\tau / b.$$

Strictly speaking, the apparent inclination of the stimulus line would itself be decreased in proportion to the extent to which cyclofusional movements have taken place as a response to the declination between the images. This can be readily observed.[13] For small cyclofusional movements, however, the observer is usually unaware of any decrease in the inclination of the stimulus line. On the other hand, cyclotorsion may have an adverse effect on depth perception.[21] Thus, one cannot account for the Verhoeff effect on the basis that cyclofusional movements are responsible for the decreased depth effect, since this would imply that the more unequal the luminances of the retinal images are made, the greater would be the stimulus to cyclofusional movements, which, as will be shown, is not true.

Results.—The stimulus line was inclined in steps of 10, 20, and 30 arc degrees from the vertical, at one time with top toward and at another time with top away from the subject. For each inclination a series of filters ranging from 50% transmission to 0.05% transmission were placed before one eye or before the other to reduce the luminosity of the image of the stimulus line.

1. When the inclination of the two beads was adjusted so that they appeared parallel to the stimulus line, it was found in every instance, for three observers, that as long as the stimulus line could be seen by both eyes at all, the setting of the inclination of the beads was identical (plus or minus 1 arc degree) with the inclination of the stimulus line; that is, there was no decrease in the apparent stereoscopic inclination of the stimulus line with difference in luminosity between the images in the two eyes. This result does not agree with the calculated inclinations found by Dyckerhoff and Siebeck,[12] who reported that the apparent inclination of the test line was never equal to that of the stimulus line and that it tended to be less the greater the darkening of the image of one eye. The data presented here show that a change in the luminosity of the image in one eye has not resulted in a change in the physiologic disparity between the images.

2. When the two beads were so adjusted that they appeared stereoscopically vertical, the degree to which their actual inclination was not vertical was a measure of the degree of cyclotorsion of the eyes. There were some individual differences in the results and in the magnitude of the cyclotorsional movement. One individual showed a cyclotorsion when the stimulus line was tilted away at the top, but not when it was tilted forward. This result may be due to a tendency to a cyclophoria. However, rather typical results are shown for two observers in Figure 4, where the stimulus line is inclined 20 arc degrees, with the top away from the observer. The measured inclination of the beads in arc degrees

§ This relationship can be easily derived. It can be found, however, in Helmholtz's Treatise on Physiological Optics, Volume III, and as translated by J. P. C. Southall in 1924 on page 349 (Optical Society of America).

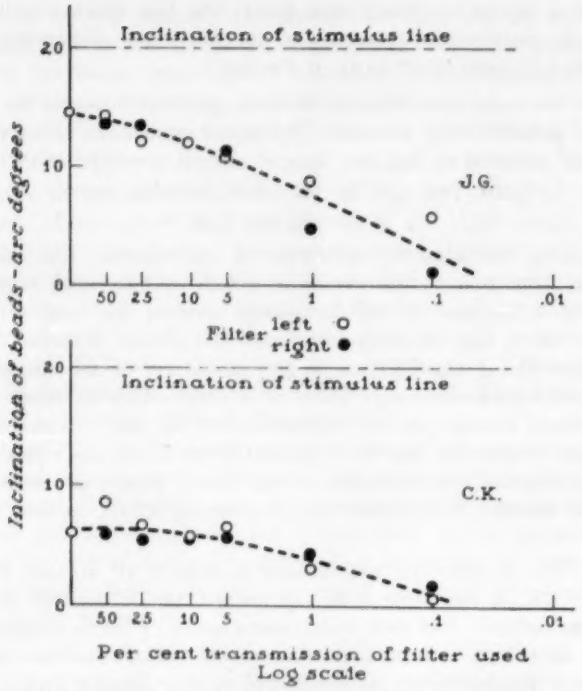

Fig. 4.—Illustration of the part played by cyclofusional eye movements from an inclined stimulus line, when the image of one eye is darkened by filters of various transmissions. The data are the inclinations of the test beads when they appeared vertical.

is plotted on the ordinate, and the per cent transmission of the filter used before one and the other of the eyes is plotted on the abscissa in decreasing logarithmic units.

It is clear that the stimulus for a cyclofusional movement from the declination between the images caused by the inclination of the stimulus line is affected by the difference in luminosity of the images of that line between the two eyes. For filters having a transmission near 0.10%, the stimulus line was no longer visible to one eye, and no cyclotorsion could be measured. For small difference in luminosities, the degree of cyclotorsion remains about the same. When a cyclotorsion of the two eyes does occur, the actual effective declination, δ_p, would be less than the declination, δ_s, owing to the inclination of the stimulus line alone ($\delta_p = \delta_s - \tau$). Hence, one would expect the stimulus line to appear less inclined when the cyclotorsion is larger.[14] The maximal cyclotorsion occurs when the luminosities are equal. Most subjects are generally unaware of an increased inclination of the stimulus line as the difference in luminosities increases, partly because in the fused image of the line some of its normal character is lost. As one of the results of this study, it was found that decreasing the luminosity of the image in one eye does decrease the stimulus for cyclofusional movements.

3. Verhoeff had reported that, in addition to a "decrease in apparent depth" when a difference in luminosities of the retinal images was introduced, there was a lateral inclination or deviation of the binocular image in the sense of a tilt in the frontoparallel plane toward the brighter image. This apparent lateral

inclination was found by Dyckerhoff and Siebeck, and was observed as well in our study—however, not unequivocally—for our three observers. The effect occurred only for the denser filters, and whether it occurred seemed to be related to the ocular dominance. This apparent lateral inclination is, of course, an aspect of the general problem of the apparent subjective direction of fused disparate images.[22] While this apparent shift in the lateral inclination is an important phenomenon, the problem in which we are interested here is only that pertaining to disparity and to the resultant stereoscopic depth.

III

In the two experiments described in the preceding sections, the adaptation levels of the two eyes were maintained the same. It is possible that the Verhoeff effect may result only from experimental set-ups in which the adaptation level for the whole field is different for each eye, as it was in his experiment where black lines drawn on illuminated white backgrounds were used. A filter inserted before one eye reduced the entire adaptation level for that eye. On the other hand, the luminosity of the stimulus line itself could not be affected by the filters, except so far as irradiation effects would occur.

Apparatus was set up in this part of the study to duplicate the conditions of the original Verhoeff experiment, and at the same time the experimental set-up was arranged not only so that one could measure the apparent inclination of the perceived line in space, as did Dyckerhoff and Siebeck, but in addition so that there could be determined the cyclotorsional positions of the eyes under the influence of the declination of the images.

Apparatus.—The basic apparatus was a haploscope (Fig. 5 is an exaggerated schematic drawing) with which 50% transmission-50% reflection mirrors were used. The targets were placed 56 cm. from the eyes and were suitably screened by circular apertures so that the edges of the targets could not be seen. In front of the mirrors, also, and 56 cm. from the eyes, was mounted the frame supporting

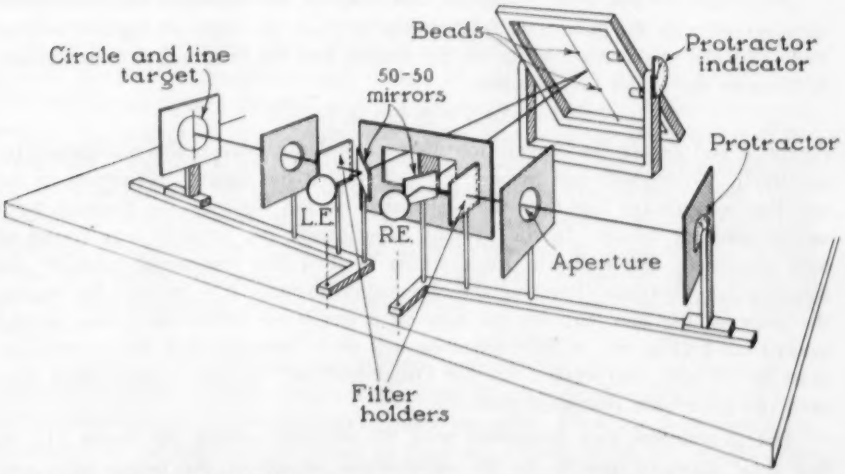

Fig. 5.—Sketch of haploscopic arrangement set up to duplicate the Verhoeff observations, with a means of measuring the apparent inclination of the fused haploscopic images.

the separated beads, as in the preceding experiment. This frame could be inclined about a horizontal axis by the subject by means of a hand wheel. The angle of inclination was read from a suitable protractor scale by the experimenter. As before, the beads were separately illuminated by lamp housings attached to the frame. An aperture and septum restricted the visual field in front of the haploscope to the beads, which were seen against a black background. The experiment was conducted in a dark room.

The detail on the targets, which were also separately illuminated (luminosity by reflection from mirrors about 10 millilamberts), was that used by Verhoeff, consisting of a near vertical line and a circle (10 cm. in diameter) drawn with India ink on heavy white cardboard. Each of the targets could be turned about an axis at right angles to the target and through the center of the circle, through small angles, to cause the line to be inclined. The angle of inclination of the line measured from the vertical is the declination of the line. The total declination of the images of the lines would be the sum of the two declinations of the two targets. The apparatus was accurately adjusted by using plumb lines and telescopes. The angles (declinations) through which the targets (lines) were turned could be measured by the displacement of the image of a lamp filament projected on a meter stick as reflected by a small mirror attached to the target mounting. Angles of inclination of the target lines could be set to an estimated 5 seconds of arc.

The observer, whose head was accurately held in position in the haploscope by a suitable head rest and chin cup, on looking at the target fused the images of the two lines and circles and, if a declination was set equal on the two targets, saw a stimulus line inclined sagittally in space in the median plane. The plane of the circle was frontoparallel. The two beads were seen to one side of the stimulus line. By means of a hand wheel the subject could adjust their sagittal inclination so as to have them appear either parallel or stereoscopically vertical. Again the beads were used as the test device, for they did not introduce another stimulus for cyclofusional movements of the eyes.

Procedure.—First, a determination was made of the extent to which empirical data agreed with the geometric relationship between the angle of sagittal inclination, i, of the stereoscopic image of the targets and the total angular declination, δ, between the target lines, namely

$$\tan i = b \tan \delta/2a.$$

Again, b and $2a$ are the observation distance and the interpupillary distance, respectively. Dyckerhoff and Siebeck [13] reported that the sagittal inclination of the test line was always less than that calculated on the basis of the formula by a nearly constant factor. In the present experiments the formula was found to hold absolutely. So well was the formula verified that one could calculate the interpupillary distance (knowing the observation distance $b = 56$ cm.) by finding the slope of the line that fits the data on a graph on which $\tan i$ was plotted against $\tan \delta$ (Fig. 6). A little reflection will show, however, that this verification must be the case, and were it not for Dyckerhoff and Siebeck's paper these data need not have been discussed here.

The experiment then proceeded with the subject's setting the beads (1) so that they appeared parallel to the stereoscopic image of the target lines and (2) so that they appeared stereoscopically vertical (to measure the degree of

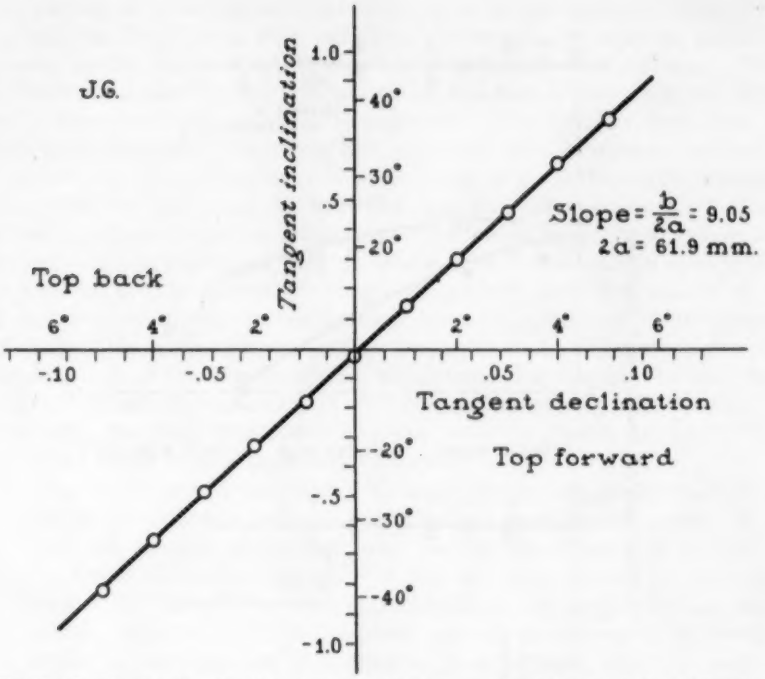

Fig. 6.—Graph showing the linear relationship between the tangent of the inclination of the fused images and the tangent of the declination of the haploscopic images.

cyclotorsion), when a series of neutral-tint filters from 50% to 0.1% transmission were inserted before one eye or the other or both eyes (See Fig. 5), so as to reduce the luminance of the retinal image. In this instance the light-adaptation level for the eye would be changed by the filter, because the luminosity of the background would be affected by the filter.

Results.—1. It became clear at the outset that, when the beads were set apparently parallel to the stereoscopic image of the inclined haploscopically seen lines, inclination agreed exactly, within 2 arc degrees, for all of four observers, with the formula given above, regardless of the filters used or declinations of the target lines (Fig. 7). This was true so long as both lines were perceivable, and they were perceivable for filters whose transmission was greater than about 0.1%. Thus the apparent inclination of the fused stereoscopic images was unaffected by decreasing the luminosity of the image in one eye; that is, there was no change in the physiologic disparity stimulus when the luminosities of the images in the two eyes were made unequal. The Verhoeff stereoscopic effect could not be verified.

It must be made clear that experiments such as this one do not measure an "absolute" subjective depth (inclination), since absolute depth can be only a subjective experience in visual space and is unmeasurable. Here the disparities from the images of the beads are adjusted to equal the disparities of the images from the stimulus lines in order that each may give the same inclination. If a partial cyclofusional movement has taken place, the subjective depth inclination will

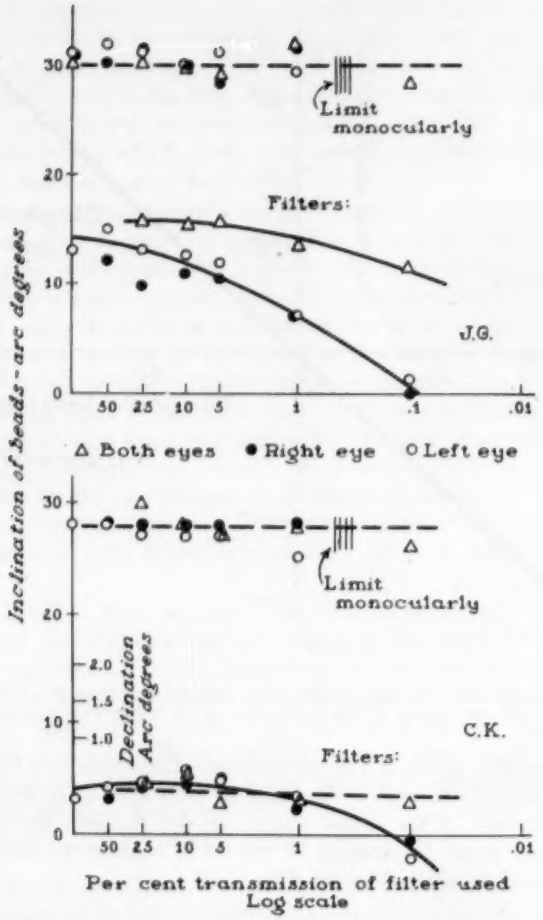

Fig. 7.—Illustration of the extent to which cyclofusional movements of the eyes occurred in the stereoscopic observations of tilted lines in the haploscope. The upper sets of data are for the inclination of the beads when they appeared parallel to the fused images of the haploscopic target lines. The lower sets are for the beads set apparently vertical.

be reduced in proportion, but the setting of the beads for apparent parallelism to the stimulus lines will not reveal this fact, but rather will duplicate the disparity condition of the stimulus lines. If, however, the geometric disparity (less cyclotorsion) were modified physiologically by the action of the filters, as maintained by Verhoeff, this fact should be found in the decreased angle of inclination of the beads when set parallel, since these beads were unaffected by the filters. No such decrease was found in any of the experiments.

2. When the inclination of the line determined by the two beads was adjusted so that it appeared stereoscopically vertical, a measure was obtained of the degree of cyclofusional torsions that the eyes have made. Figure 7 shows the results of two observers when the stimulus (haploscopic) lines produced a stereoscopic line image inclined 30 arc degrees from the vertical (top away) and when different neutral-tint filters were used before one or the other eye and before both eyes.

Inspection of these graphs shows again, as in the preceding experiment, that a cyclotorsion does occur, with individual differences, and that its magnitude decreases as the luminosity difference between the two eyes increases. When this difference became greater than 0.1%, no cyclotorsion was measured. However, if filters with the same transmission were placed before both eyes, the cyclofusional movement was only a little decreased with decrease in luminosities of both images. This difference must be explained on the basis that the adaptation levels of the two eyes were the same and thus the corresponding thresholds of contrast perception were also identical. When filters were placed before both eyes, the adaptation levels of both decreased, with a resultant increase in contrast perception. The haploscopic observed lines were thus seen equally by the two eyes, and the stimulus to cyclofusional movements persisted. With unilateral darkening of the image, this situation no longer obtained: The much higher light adaptation level of the one eye affected the contrast discrimination of the other.‖ So, at a 0.1%-99.9% darkening of the image of one eye compared with that of the other the black haploscopic line was no longer visible against its background and vision became essentially monocular.

3. The crucial part of the original Verhoeff observations consisted of placing the filter so as to darken only the lower half of the stimulus pattern of one eye. Then the stimulus haploscopic fused line no longer appeared straight but rather broken at the center (Fig. 1). The original report stressed the observation not only that this "break" was a lateral inclination of the darkened image toward the brighter image but also that the lower part of the line appeared bent back (less inclined), corresponding to a decrease in stereoscopic depth for that part of the line.

The filter holders of the present apparatus were lowered so that only the lower half of the haploscopically seen target would be seen through the filter by one eye. Again, the subject was asked to adjust the beads (1) so that they appeared to be parallel to the stereoscopic image of the upper half, (2) so that they appeared to be parallel to the stereoscopic image of the lower half, and (3) so that they were subjectively vertical.

It was found without exception by four observers that when the beads were set to appear parallel to the upper half of the inclined haploscopically seen line, they were also parallel with the lower (darkened) half. This observation was true as the denser filters were used, until the point was reached where the line in the lower half of the target could not be discriminated. Then there was no depth for that half and the line was indefinitely localized fore-or-aft, with no stereoscopic depth.

The lateral inclination of the lower half toward the brighter image was generally observed, but not unequivocally, for there were individual differences. If the undarkened image was seen by a strongly dominant eye, the lateral inclination was striking, especially as the higher density filters were used. When the undarkened image was seen by the nondominant eye, the lateral inclination was less obvious. One subject reported that she could see the lateral inclination only with difficulty and with effort, and then only when the denser filters were used. Since this lateral inclination concerns the problem of the subjective direction of the fused disparate images rather than the stereoscopic response, it will not be considered further here.

‖ References 23-25.

From these experiments one would have to conclude that decreasing the luminosity of the image of one eye does not alter the physiologic disparity between the images of the two eyes or the stereoscopic depth. This conclusion is, of course, only true for static spatial line configurations. One must ask, then: What is the explanation of the observations made by Verhoeff and corroborated as well by other subjects? It is possible that the lateral inclination of line toward the brighter image may have interfered with the stereoscopic depth. It is also possible, since the effect was found only with relatively dense filters, that the differential contrast threshold of the eye seeing the darkened target became too high for the line to be readily visible. However, the answer most probably lies in the fact that, as so often is the case, the results of introspective observation can be misleading, for, when one attempts to measure the observed phenomena, they often are not found. This statement generally emphasizes the danger of making too sweeping a conclusion from introspective observations made from figures drawn to be seen in a stereoscope.

Summary

The previously reported observations that stereoscopic depth from static spatial line configurations was reduced when the image of one eye was darkened by a filter were reexamined by means of three experimental arrangements in which one could measure the amount of reduction, if any, that occurred. The results of all three experiments could not verify the original observation, and it was concluded that the disparity between images, even though the luminance of one of the half-images was markedly decreased, maintains its integrity, and the stereoscopic depth resulting therefrom is stable.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted, and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest, and be accompanied with photographs whenever possible.

BILATERAL POSTERIOR UVEITIS COMPLICATING A POSITIVE TUBERCULIN CUTANEOUS REACTION

BILATERAL inflammation of intraocular structures certainly is a rare complication of a positive tuberculin reaction. However, Muncaster and Allen [1] have reported the case history of a school teacher who decided to take the tuberculin tests when her students were being screened. She developed a positive reaction following the second strength and 10 days later showed bilateral uveitis. The inflammation cleared within three months.

Weizenblatt [2] saw a very interesting case. The patient developed a bilateral cyclitis and neuroretinitis four days after the appearance of a positive tuberculin reaction. The inflammation subsided over a period of some weeks. Six and a half years later the patient had another tuberculin test, a second positive reaction at site of the injection, and a recurrence of bilateral cyclitis and neuroretinitis. With the administration of atropine and the passage of time, the second bout also cleared, with residual normal vision.

The patient reported would seem to belong in the same category as the above cases.

Report of Case

A single white man, 29 years of age, was admitted to the VA Hospital, Rutland Heights, Mass., Jan. 11, 1956. The chief complaint was pain in right side of chest and hemoptysis. He had suffered with "pneumonia of the bronchial type" in October, 1955. In December a chest x-ray showed a patch of consolidation in the right upper lung.

On admission examination x-ray of chest showed clearing of the shadow in right upper lung. Temperature, pulse, and respirations were normal; physical examination, essentially normal.

Jan. 23, 1956, the patient received a tuberculin intradermal test in the left forearm. Test material was purified protein derivative of tuberculin U.S.P. (tuberculin P.P.D.) (Parke, Davis) (0.00002 mg. for the dose). The following day he showed a positive reaction to the P.P.D. with pain, tenderness, redness, and swelling at site of injection, red streaks up the arm to the elbow, tender swollen nodes in the left axilla. He showed fever (temperature 100 F); pulse rate was 96.

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The reaction subsided gradually, but on Feb. 8 (16 days after intradermal P.P.D.) he developed pain and redness of the right eye. Four days later the left eye showed a similar reaction.

The eye findings were those of acute bilateral inflammation of the posterior uvea. The patient complained of blurred vision, photophobia, pain in eyes, and lacrimation. Objective findings included bulbar injection (but definitely not circumcorneal), keratic precipitates, aqueous flare, and vitreous opacities. The irides were normal except for one transient posterior synechia, O.S., at 7 o'clock. Fundi were hazy, but disc margins were distinct. No exudates or hemorrhages were seen.

Visual acuity deteriorated to O.D. 6/12; O.S. 6/16.

The patient was treated with hot boric acid compresses to the eyes and 1% atropine drops t.i.d., O.U. Improvement was slow but definite. By March 8 the eyes were white and quiet. Vision had improved to 6/5 O.U. Aqueous flare had disappeared. The keratic precipitates and vitreous opacities were much less marked. No exudates or hemorrhages were seen by ophthalmoscopy.

Summary

A case of uveitis following intradermal tuberculin is presented, suggesting a causal relationship.

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Annual Reviews

GLAUCOMA, 1955-1956

BERNARD BECKER, M.D.
St. Louis

I. The Facility of Aqueous Outflow
- A. Measurement
- B. Site of Resistance
- C. Nature and Modification of the Resistance
  1. Experimental
  2. Clinical
     (*a*) Glaucoma Diagnosis
     (*b*) Evaluation of Therapy

II. The Rate of Formation of Aqueous Humor
- A. Theory and Measurement
- B. Alterations
  1. Spontaneous Variations
  2. Carbonic Anhydrase Inhibition and Aqueous Flow
  3. Other Pharmacologic Agents That Influence Secretion
  4. Surgical Means of Changing Aqueous Flow Rate

III. Episcleral Venous Pressure

IV. Miscellaneous Glaucoma Topics

THE EXCELLENT glaucoma abstract services provided by *Excerpta Medica*, the *American Journal of Ophthalmology*, and *Ophthalmic Literature* make it quite unnecessary for this review to reiterate the essence of each publication recorded during the past year. Rather, the few concepts listed above have been selected for review as underlying much of the current thinking and research related to the glaucomatous disorders.

Recent work on glaucoma has emphasized in exemplary fashion the proximity of the laboratory and the clinic. It has demonstrated the benefits to be derived from close collaboration of the clinician and the research worker in the approach to disease processes. The names of investigators and the details of their experiments have been sacrificed in the revision of this review in order to direct efforts to an integration of available data and its established conclusions as well as its uncertainties and unanswered questions. Unfortunately, this undertaking has been necessarily limited, not only by the accomplishments of workers in this field but by the inadequacies of interpretation and understanding as well as the prejudices of the reviewer.

When intraocular pressure is stabilized, the rate of formation of aqueous humor is equal to its rate of exit from the eye. As formulated by Goldmann,[258] this rate, F, is proportional to the outflow pressure gradient, that is, the difference between intraocular pressure, P_o, and episclear venous pressure, P_v. This may be expressed by the following equation:

(1) $F=C(P_o-P_v)$

If pressures are expressed in millimeters of Hg and flow in cubic millimeters per minute, then the constant, C, is Grant's[266] coefficient of "facility" of aqueous outflow (the reciprocal of Goldmann's "resistance" to aqueous outflow). When equation (1) is written in the form

(2) $P_o=F/C+P_v$

it is apparent that the abnormalities in intraocular pressure that characterize the glaucomatous state, as well as alterations induced by therapy, may be discussed

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in terms of changes in (I) C, the facility of aqueous outflow; (II) F, the rate of formation of aqueous humor, and (III) P_v, the episcleral venous pressure.

I. The Facility of Aqueous Outflow (C)

With repeated emphasis on the decreased facility of outflow (increased resistance) which has been found to characterize almost all types of glaucoma,* considerable interest and effort have been devoted to an elucidation of the site and nature of this obstruction as well as its modifications.

A. Measurement of Facility of Aqueous Outflow

1. *Perfusion.*—Using perfusion methods in enucleated normal human eyes, the persistence of average values for outflow resistance in vitro of comparable magnitude to that observed in vivo by tonography has been demonstrated.† Similar in vitro measurements on glaucomatous eyes have revealed that the reduced facility of outflow persisted after enucleation. These observations have been confirmed ‡ and have provided most important support for the validity of in vivo methods of measurement as well as for concepts of the stable nature of the resistance in normal and glaucomatous eyes. In addition, the perfusion technique has permitted the study of outflow resistance and its modifications in the enucleated eyes of cattle, pigs, rabbits, and cats.§

Similar perfusion techniques have been used in vivo to obtain estimates of outflow facility on the living eyes of animals and a few patients.[71] These were in close agreement with subsequent determinations in vitro as well as approximating the preceding tonographic values on the same eyes.

2. *Tonography.*—Tonography has received considerable attention and widespread clinical acceptance during recent years.‖ It has provided a practical means of measuring directly the facility of outflow in human eyes. The application of tonography to rabbit eyes [365] has opened a new chapter in the study of aqueous flow. By this means an opportunity has been afforded for verifying the assumptions of tonography by a direct comparison with in vivo and in vitro perfusion values on the same eye.[71] It has also provided an adaptable method for the study of effects of various pharmacologic agents and surgical procedures on outflow resistance and rate of aqueous formation. These will be discussed in more detail below.

A number of sources of error have been described as inherent in the unphysiologic condition induced by placing a weight on the eye. These as well as inaccuracies in instrumentation and calibration have been reviewed.¶

In Grant's formulation, an average normal value for scleral rigidity was utilized. The importance of deviations from average values for scleral rigidity have been explored and emphasized.# Corrections for scleral rigidity have been difficult to apply because of inaccuracies in measurement. Furthermore, rigidity of the sclera has been demonstrated to affect both the volume of distention of

* References 75, 183, 228, 229, 256, 267, 268, 274, 368, 492, 493, 635, and 645-647.

† References 273 and 275.

‡ References 228 and 229.

§ References 40, 42, 44, and 46.

‖ References 60, 66, 75, 106, 183, 191, 260, 266, 267, 274, 362, 368, 532, 567, 568, 572, and 614.

¶ References 34 and 75.

References 35, 76, and 234.

the globe by the tonometer and the estimates of the intraocular pressure. Thus, variations from normal scleral rigidity have markedly distorted the slopes of tonographic tracings and the estimates of outflow facility. In clinical use, tables and graphs [35] have proved most helpful for correcting this source of error. For measurement of scleral rigidity, a tonometer adapter has been devised so as to permit interchange of weights more readily without change in tonometer position.[426] Fortunately, it has proved essential to correct for abnormal scleral rigidity in clinical tonography only in borderline and unusual instances.[34] For example, increased scleral rigidity has become an important point in the differential diagnosis of hypersecretion glaucoma.[76]

Corrections for the increase in episcleral venous pressure induced by the weight of the tonometer on the eye during tonography (an average rise of approximately 1.25 mm. Hg)[412] are readily applied and have been incorporated in newer tonographic tables. Variations from normal corneal curvature and abrupt changes in blood pressure are easily detected and suitable corrections can be applied.[75]

With these corrections, the remarkable agreement of tonographic, perfusion, and turn-over measurements of facility of outflow in the normal human or rabbit eye has suggested that other sources of error are probably small.*

Although the placing of a tonometer on the eye might have influenced secretion of aqueous, this effect has not appeared to be of measurable magnitude. The approach of P_t (the pressure in the eye with the tonometer in place) to the estimated P_o (intraocular pressure in the undisturbed eye), when the tonometer has been left on the human or rabbit eye for a long period of time,† has provided additional evidence for lack of significant alterations in secretory rate during tonography.

Other methods which employ compression of the eye have been proposed for the diagnosis of glaucoma. Such suggestions as the application of heavier weights to the sclera [100] or compression at the limbus [425] or the "compensation maximum" test [353] have induced an even greater deviation from the normal physiologic conditions than has tonography. They have appeared to offer little theoretical or clinical advantage over tonography.

3. *Flow Measurements.*—As described in Section II, several methods have become available for the estimation of the rate of aqueous flow (F). From such data, facility of outflow (C) has been determined indirectly by measuring intraocular pressure (P_o) and episcleral venous pressure (P_v). Thus, from equation (1),

$$(3)\quad C=\frac{F}{P_o-P_v}$$

This has been the basis of the fluorometric method.‡ In this method it has been necessary to measure plasma and aqueous concentrations of fluorescein at various time intervals after its injection and to compute its turnover rate in the anterior chamber. With certain assumptions as to the magnitude of diffusional exchange of fluorescein, a flow constant (K_F), expressed as a fraction of the anterior chamber per minute, has been derived. The determination of the volume of the anterior chamber for the particular eye has permitted an estimate of flow rate (F) in cubic millimeters per minute. Measurements of intraocular pressure and

* References 71, 258, and 275.

† References 365 and 640.

‡ References 258 and 262.

episcleral venous pressure have provided the other two factors needed for the evaluation of the facility of outflow (C). Most significantly, this has been accomplished on the undisturbed eye by this ingenious method. The clinical application of this approach to human eyes has not received the attention it deserves, however. This has been attributed to the time-consuming and complex instrumentation and the large opportunities for error in hands less experienced than Goldmann's.§ In laboratory animals the independent measurement of aqueous flow from turn-over studies of various substances (sodium, thiocyanate, and ascorbate) has provided important data which have tended to confirm those obtained by tonography (see below).‖

B. Site of Resistance

The anatomy of the drainage channels from Schlemm's canal, as revealed by neoprene casts, has been subjected to careful study.[26] Excellent descriptions of the histology of the trabecular meshwork have been presented [120] and reviewed,[27] with essential agreement among various observers. The thesis ¶ that free communications exist between Schlemm's canal and the anterior chamber through the "internal canals" of Sondermann [564] has received support from detailed histologic observations on normal human eyes.[27] Comparable careful studies on eyes with uncomplicated chronic simple glaucoma are awaited with eager anticipation. Greater efforts must be made toward obtaining such eyes at autopsy and directing them to competent and interested pathologists.

A resistance to the outflow of aqueous humor between anterior chamber and episcleral veins has been postulated and amply verified. The precise location of most of this resistance in the normal eye has been subjected to systematic study.# The removal of the outer two-thirds of the sclera failed to alter the resistance factor in enucleated normal human eyes. Extensive incision of the trabecular meshwork and opening Schlemm's canal to the anterior chamber in one-fourth to one-third of the angle also did not decrease the resistance to outflow in most nonglaucomatous eyes. This suggested placing the site of resistance in the collector channels or aqueous veins draining immediately from Schlemm's canal. This location has found confirmation from studies on normal monkey eyes.[483] Essentially the same pressure (10% less) was recorded in Schlemm's canal as in the anterior chamber. Incising or cannulating Schlemm's canal trans-sclerally, from the outside of the eye, reduced the resistance to outflow in one human and two monkey eyes. However, as pointed out by the author,[483] this type of procedure was technically difficult and small openings into the anterior chamber may have gone undetected even in serial section. Surprisingly low resistance values were noted in the monkey eyes of these experiments even before Schlemm's canal was opened. Furthermore, it should be emphasized that the published observations have been confined to nonglaucomatous eyes.

Evidence for the collector channels as the site for resistance to aqueous outflow in glaucomatous eyes has been reviewed in detail.* On histologic grounds,† the obstruction to outflow has been placed in the scleral channels and

§ Becker, B.: Unpublished data.
‖ References 65, 242, and 352.
¶ References 589 and 591.
# References 270 and 273.
* References 22 and 23.
† References 590 and 592.

is believed to be secondary to hypertrophy and sclerosis of the sclera. Obstruction of communicating vessels in their oblique course through the sclera has also been considered as a possible site of obstruction in glaucoma.[26] An edematous process or organic vascular change in the sclera has been further postulated to account for the increased resistance to outflow in glaucoma.[357]

On the other hand, other measurements have placed the major site of resistance in the trabeculum in both normal and glaucomatous eyes.‡ Alteration in outflow resistance by hyaluronidase § and the localization of hyaluronidase-sensitive metachromatic material in the trabeculum ‖ also have suggested this site for a large part of the resistance in normal eyes. Furthermore, Schlemm's canal has been incised trans-sclerally in cannulated enucleated normal human eyes.¶ Only small (less than 20%) reductions in resistance to aqueous outflow were observed, in spite of the fact that the successful opening of Schlemm's canal to the outside was verified histologically in these eyes. In addition, it has proved possible to cannulate Schlemm's canal with polyethylene tubing in vivo in eyes with absolute open angle glaucoma and no synechiae. Under these circumstances, no significant alteration was noted in the tonographic estimates of outflow facility.# As pointed out by most writers on the subject, there has been no reason to assume that the resistance site must be the same in all eyes with open angle glaucoma or in glaucomatous and normal eyes.

In support of the hypothesis that more than one site may be involved in the obstruction to outflow in glaucomatous eyes, changes have been described in the trabeculum as well as in Schlemm's canal and its outflow channels.[588] These alterations consisted of degeneration of collagen fibers in the trabeculum and subsequent adhesions and proliferation of endothelium into and beyond Schlemm's canal. Unfortunately, the changes found appeared to be present in a number (10%) of "normal" autopsy eyes and their specificity for glaucoma has not been established. For example, artefactual adhesions of Schlemm's canal were noted in 25% of sections of normal eyes in another series.[27] Studies of the correlation of perfusion data with histologic appearance of routine autopsy eyes should help resolve this most basic problem.

It is clear that the available data are entirely inadequate on eyes with uncomplicated glaucoma, and the problem of the site or sites of resistance even for normal eyes remains unsolved.

In closed angle glaucoma and in most of the secondary glaucomas the site of the obstruction has been more apparent and there has been reasonable agreement among workers in this field.

The degree of reduction of outflow facility has been found to be proportional to the extent of synechial obstruction seen gonioscopically in the glaucoma following flat anterior chambers.* The obstruction to outflow in phacolytic glaucoma was believed to be caused by the histiocytic response to the liquefied lens material, with macrophages blocking the trabeculum.† It was emphasized that lens extrac-

‡ References 262 and 413.
§ References 44 and 46.
‖ References 27 and 115.
¶ Keskey, G. R.: Unpublished data, 1955.
# Becker, B.: Unpublished data.
* References 267 and 372.
† References 213 and 587.

tion was curative in this condition. The nature of the obstruction in posteriorly dislocated noncataractous lenses or in small malignant melanomas of the choroid remains obscure, however.

The clinical course and therapy of the progressive obstruction by synechiae in subacute types of closed angle glaucoma have been reviewed.[136] Attention has been drawn to the more frequent occurrence of synechiae and angle closure in the upper angle and its progression to include the lower angle.‡ The occasional eye with chronic simple glaucoma and an anatomically narrow angle has caused considerable confusion as to classification and therapy.[288] Such a diagnosis can be readily established, however, by the tonographic finding of a decreased outflow facility out of proportion to the gonioscopic evidence of obstruction.

In an outstanding series of papers during the past year, the development of the normal angle has been described.§ These data have provided an explanation for many of the anomalies seen on gonioscopy. A cleavage defect was suggested as the causative factor in congenital glaucoma rather than the previously accepted concept of persistence of mesodermal remnants. The tonographic evidence of obstructed outflow in congenital glaucoma ‖ would thus appear to be readily explained by a pretrabecular block.

An interesting variant of essential iris atrophy characterized by unilateral corneal dystrophy with edema, peripheral anterior synechiae, and obstructed outflow with glaucoma has been reported.[137] In these cases there was only slight atrophy of iris stroma, without hole formation or pupillary displacement. The relationship of functional status of corneal endothelium and the trabeculum has been highlighted by this group of patients.

C. Nature and Modifications of the Resistance to Aqueous Outflow

1. *Experimental.*—(*a*) Size of Pores: In an ingenious series of experiments, the size of the outflow channels in rabbit and human eyes has been estimated.¶ With the use of suspensions of chromium phosphate or bacteria, evidence was found that particles up to 1.2μ to 2.4μ pass through the angle of the anterior chamber of rabbit eyes. Comparable values in human eyes were 1.5μ to 4.4μ. The injection of colloidal thorium dioxide (Thorotrast) or Angiopac (colloidal suspension of diiodostearate in dextrose solution) into the anterior chamber of monkey and human eyes at a pressure of 25 mm. Hg and study of the microradiographic pattern of the angle have resulted in estimates of the diameters of the orifices from the trabeculum into Schlemm's canal at between 1.5μ and 2.25μ.[226] Recently the possibilities of injecting radiopaque material into the anterior chambers of living rabbit eyes have been described and the outflow channels have been followed radiographically.[145]

(*b*) Hyaluronidase and Resistance to Outflow: The elegant experiments from Barany's laboratory have resulted in some of the most provocative reports to appear in recent years.# With use of the perfusion technique, the nature of the resistance has been explored by attempts to alter it with pharmacological agents. Most interesting has been the finding that hyaluronidase added to the perfusion fluid causes a decrease in resistance by about 50% in the enucleated eyes of

‡ References 485 and 486.
§ References 8, 9, 111, and 121.
‖ Reference 475; Becker, B.: Unpublished data.
¶ References 320 and 321.
# References 40, 44, and 46.

cattle, rabbits, cats, and pigs. These findings have been amply verified.* However, no evidence could be obtained for the presence of hyaluronidase-like enzymes in normal aqueous humor.† The effects of hyaluronidase on rabbit eyes in vivo have been difficult to assess because of the complicating inflammatory response which has followed the injection. Thus, no effect on intraocular pressure in rabbit eyes was noted following the injection of hyaluronidase into the anterior chamber, but at doses of 10 TRU per cubic centimeter iritis and kerectasias appeared.[408] However, no adverse affects, except mild iritis, have been reported following the intracameral injection into rabbit eyes of 25 VRU of a more purified hyaluronidase.[7] Transient falls in intraocular pressure in patients had been noted following subconjunctival injections of crude hyaluronidase preparations.‡ A lowering of introcular pressure in two patients with secondary glaucoma followed the intracameral injection of hyaluronidase,[408] but this might have resulted from the paracenteses. Hyaluronidase infusion has produced a much smaller and less consistent alteration in outflow facility in enucleated normal human eyes than in normal animals.§ Unfortunately, the markedly impaired outflow facility of enucleated glaucomatous human eyes has not been altered by hyaluronidase infusions.‖

The site and nature of the hyaluronidase-sensitive substance in the outflow channels remains a most important subject for investigation. It has been suggested that hyaluronic acid is carried forward from the vitreous following postmortem changes in enucleated eyes.¶ However, mucopolysaccharides have been demonstrated in histologic sections of the trabeculum of human eyes, as evidenced by such staining procedures as periodic acid-fuchsin, alcian blue, or metachromasia with toluidine blue.[115] Following treatment with hyaluronidase in freshly enucleated eyes, no change in periodic acid-fuchsin staining was noted but metachromasia and alcian blue staining of the trabecular meshwork were altered. This suggests the occurrence of a hyaluronidase-sensitive polymer in the trabeculum and agrees well with Barany's findings. No alterations in particle filtrate curves were detected when hyaluronidase was infused into enucleated eyes.[322] However, this has not contradicted the measured increase in facility, since the particle method used did not measure relative quantities carried by the smallest openings. On the other hand, microradiographic evidence of enlargement of the trabecular clefts and their orifices into Schlemm's canal following hyaluronidase injection has been described.[227]

(*c*) Other Agents That Modify Outflow Resistance: The effects of anesthesia upon outflow facility have been studied in rabbits and patients. In rabbits subjected to tonography, an increase in facility of outflow and a fall in intraocular pressure was induced by the administration of pentobarbital or paraldehyde anesthesia.[576] Similar increases in outflow facility have been noted after urethan

* References 72, 229, and 653. Beswick, J. A., and McCulloch, C.: The Effect of Hyaluronidase on the Viscosity of Cattle Aqueous Humor, read before the East Central Section of the Association for Research in Ophthalmology, Toronto, Canada, Jan. 9, 1955.

† References 46 and 441.

‡ Moor, W. A., and Shahan, P. T.: Spreading Factors in Ophthalmology, read before the Midwest Section of the Association for Research in Ophthalmology, St. Louis, Nov. 17, 1947.

§ References 229 and 273; Becker, B., and Constant, M. A.: Unpublished data.

‖ Becker, B., and Constant, M. A.: Unpublished data.

¶ Beswick, J. A., and McCulloch, C.: The Effect of Hyaluronidase on the Viscosity of Cattle Aqueous Humor, read before the East Central Section of the Association for Research in Ophthalmology, Toronto, Canada, Jan. 9, 1955.

administration during perfusion in rabbits.[42] These findings emphasize the necessity of rigid anesthetic control in studying the modification of aqueous humor dynamics in rabbit eyes. Studies carried out on rabbits not subjected to general anesthesia have proved most satisfactory.#

In glaucomatous human eyes, an increase in facility and a fall in intraocular pressure following intravenous thiopental sodium was noted.[184] This raises the interesting question of interpretations of tonograms on children's eyes done under anesthesia.

Attempts have been made to duplicate the glaucoma associated with epidemic dropsy by the administration in vivo of argemone oil or sanguinarine to monkeys.* Preliminary data revealed a rise in intraocular pressure as well as a proliferation of endothelium in the trabeculum and Schlemm's canal. Unfortunately, similar, but less marked, changes were noted in a control animal. Transient rises in intraocular pressure in rabbits have been described following intracameral, subconjunctival, subcutaneous, or intravenous injections of sanguinarine.† It will be recalled that sanguinarine has been demonstrated to decrease outflow facility when perfused through ox eyes in vitro.[292] Tonographic tracings would be of considerable interest in rabbits and monkeys injected in vivo. Perfusion data on the enucleated eyes of such animals might confirm the histologic findings and reveal the extent of the disordered outflow.

Of several enzyme inhibitors studied,[40] iodoacetate has been one of the few observed to alter resistance in cattle eyes in vitro. This is of particular interest, since this radiomimetic agent has been demonstrated to be cataractogenic [142] and endothelial damage of the corona occurs after intracameral injection of idoacetate.‡ Since the endothelial cells of the trabeculum have been considered to be a prolongation of the corneal endothelium,[524] these findings have stimulated considerable speculation. However, attempts to alter outflow resistance in normal enucleated human eyes by iodoacetate infusion have proved unsuccessful.§

Hormonal influences on outflow facility are suggested by the cyclic changes of the menstrual cycle.[75] The large increase in outflow facility during pregnancy accounts for the ocular hypotension reported.[438]

An intriguing relationship between outflow facility and the depth or volume of the anterior chamber has been noted in enucleated animal and human eyes.‖ Thus, varying the anterior chamber volume of the enucleated eye results in a linearly related alteration in facility of outflow. Pertinent to these findings is the report that in vivo and in vitro perfusion data for guinea pig, rabbit, and cat eyes have revealed similar values for intraocular pressure but enormous variation in outflow facility values (0.08 for guinea pigs, 1.54 for cats).[72] However, the facility variations proved to be roughly proportional to the volumes of the anterior chambers of the very different-sized animal eyes studied. Thus, the linear relationship between the facility of outflow and volume of the anterior chamber appears to hold true not only for individual human or animal eyes but also among species. These data were found to be in excellent agreement with the similar coefficients of aqueous secretion measured in all of these species when

References 63, 70, 242, and 352.
* References 388 and 418.
† References 292 and 406.
‡ Cibis, P. A.: Personal communication to the author.
§ Becker, B., and Constant, M. A.: Unpublished data.
‖ References 72, 228, and 496.

secretion is expressed as a fraction of the volume of the anterior chamber.¶ Thus, a mechanism is available in the eye for maintaining relatively uniform concentrations rather than total amounts of constituents of the aqueous humor.

Direct evidence has been obtained that the alterations in outflow facility induced by hyaluronidase are not dependent upon or affected by changes in anterior chamber volume.[72] Thus, these two mechanisms for changing the resistance to outflow from the anterior chamber of enucleated eyes appear to be entirely independent of one another.

A suggestive relationship of anterior chamber volume to outflow resistance in a group of human eyes may be seen in Goldmann's data.[258] Correlations of tonographic outflow facility with variation in depth of the anterior chamber have been described in two patients with secondary glaucoma.# However, it is certainly true that many eyes with extremely shallow anterior chambers have normal outflow facility values.* The clinical significance of anterior chamber volume alterations and their effect upon facility of outflow needs further study.

(*d*) Compensatory Changes: One of the interesting relationships noted in the tonographic study of rabbit and human eyes has been the interrelationship of alterations in rate of formation of aqueous humor and the facility of outflow. In a number of instances these changes have appeared to be of such a nature as to maintain intraocular pressure by compensatory means. Thus, a decrease of aqueous production has been recorded on the homolateral side following unilateral carotid ligation in rabbits.[365] This decrease in aqueous flow is partially compensated by decreased outflow facility, thus tending to maintain intraocular pressure. Similar increases in resistance to aqueous outflow have persisted in enucleated rabbit eyes after homolateral carotid ligation.[40] When animals with unilateral carotid ligation were subjected to water-drinking, the eyes on the ligated side were reported to respond with greater increases in intraocular pressure than the unoperated on, contralateral eyes.[143] These latter findings need confirmation; for here were induced facility changes and response to water imbibition in rabbits which closely resembled the status of human eyes with chronic simple glaucoma.

Compensatory decreases in outflow facility of rabbit eyes have been observed when secretion was depressed by some 60%.[149] This occurred after the administration of phentolamine methanesulfonate, chlorpromazine, or vasopressin. A partial suppression of aqueous humor secretion and compensatory decrease in facility of outflow were also noted following the administration of *p*-aminohippuric acid to rabbits. Cervical sympathetic ganglionectomy prevented the outflow changes on the side operated on. Thus, although secretion was decreased equally in both eyes, intraocular pressure fell more significantly on the uncompensated sympathectomized side.[387]

Similar compensatory lowering of outflow facility has been observed following the partial suppression of aqueous flow by acetazoleamide in rabbits.[70] Coincidentally, this finding helped to resolve the problem of the so-called acetazoleamide-"resistant" rabbits. The unresponsiveness of such rabbits to carbonic anhydrase inhibition in terms of intraocular pressure measurements was demonstrated to represent the compensatory shutting down of the outflow mechanism in spite

¶ Reference 41; Becker, B.: read before the Macy Foundation Conference on Glaucoma, Dec. 5, 1955.

References 224 and 225.

* References 34, 75, 183, 267, and 268.

of partial suppression of secretion of aqueous. By this means intraocular pressure was maintained and "pseudoresistance" to the effects of acetazoleamide was observed. Furthermore, the systemic administration of hydrocortisone or fludrocortisone was found to prevent the compensatory decrease in outflow facility following acetazoleamide. Thus, "pseudoresistant" rabbits could be converted to a "responsive" state from the point of view of intraocular pressure changes.[70] An increased responsiveness of intraocular pressure to carbonic anhydrase inhibition in rabbits was also noted following alterations of dietary sodium chloride or by systemic aldosterone administration.[349]

In normal human eyes, reductions in facility of outflow have been observed associated with the decreased formation of aqueous following intravenous sorbitol.[180] Similar decreases in facility have been recorded after depressing aqueous flow in normal human eyes by pentolinium administration.† Compensatory decreases in outflow facility following acetazoleamide administration have also been described in normal patients.‡ In glaucomatous eyes, however, the decrease in aqueous secretion induced by carbonic anhydrase inhibition does not appear to alter facility of outflow.§ This may be interpreted as a loss of the ability of the outflow mechanism in glaucomatous eyes to compensate or to recover from the compensated state.

Alterations in outflow facility in the opposite direction have also been noted. Thus, increases in outflow facility have been demonstrated after elevation of intraocular pressure in rabbit eyes.[42] The rise in intraocular pressure was produced in vivo by constricting venous outflow with a balloon-like device. The resistance to outflow as compared with the normal eye was measured in vitro and found to average 18% lower on the obstructed side.

On the other hand, glaucomatous eyes frequently demonstrate compensatory alterations of rate of secretion. Thus, in spite of the disordered outflow that characterizes the glaucomatous status, intraocular pressure may be normalized spontaneously for variable intervals because of hyposecretion of aqueous humor. For this reason, tonography proves of great value in the detection of glaucoma in such eyes. The compensatory hyposecretion which occurs so frequently in so-called "burned out" or some "low tension" glaucoma may account for the self-limited course seen in these patients.[420] It is apparent that the nature and mechanisms of such compensatory changes in normal and glaucomatous eyes need further elucidation.

The finding of nerve fibers in the trabeculum [629] and its recent confirmation [312] have provided an exciting stimulus for speculation as to its role in reflex compensatory changes and control of intraocular pressure.

2. *Clinical Alterations in Outflow Facility.*—(*a*) Glaucoma Diagnosis: Tonography has been of the greatest practical value for the direct measurement of outflow facility in human eyes. In addition to providing information pertinent to the nature of the glaucomatous disorder and the mode of action of various therapeutic agents, this technique has proved its worth in the diagnosis and evaluation of therapy of the glaucomas.‖

† Rosen, D. A.: The Effects of a Ganglionic Blocking Drug, Pentapyrrolidinium, on Ocular Fluid Dynamics: A Preliminary Report, read before the East Central Section of the Association for Research in Ophthalmology, Toronto, Canada, Jan. 9, 1955.

‡ Becker, B.: read at the Macy Foundation Conference on Glaucoma Dec. 5, 1955.

§ References 61, 62, and 272.

‖ References 34, 66, 268, and 636.

Considerable confusion exists at present as to tonometer calibration data used by different clinics. Furthermore, some laboratories correct for the rise in episcleral venous pressure during tonography [412] and for deviations from normal scleral rigidity [85] and corneal curvatures,¶ whereas other observers fail to do so. Differences in edge curvature of the plungers of electronic tonometers,# the variation in facility values obtained using different weights,* and the value of episcleral venous pressure to be used in calculating rate of aqueous flow provide additional sources of variation among laboratories. Rather than review the opinions and usages of various investigators, it would seem preferable to hope that these differences will be largely resolved by more accurate calibration data and more rigid tonometer specifications. They can then be more readily summarized and discussed in next year's review. The variations in details of calculation and corrections alter absolute values, but they do not detract from the empirical clinical value of tonography, however.

No differences in tonographic values have been noted in comparing white and Negro populations.† In one series of patients, a greater resistance to aqueous outflow has been recorded in left eyes than in right eyes.[108] However, this has not been the experience of most other laboratories.

A decrease in tonographic outflow facility with age has been reported to occur apart from demonstrable pathologic changes.[653] This has been the experience of some other tonographic laboratories ‡ and agrees well with fluorometric measurements.[258] However, other observers have noted no such variations of facility with age.§

The reports of increased resistance with age might have resulted from the manner of selecting cases (e. g., inadvertently including borderline glaucomas in the older group of patients). On the other hand, the histologic findings [588] of trabecular changes in over 10% of the older population have suggested that disorders of outflow are more common than was suspected. Another source of low facility values in elderly patients may be related to secretory failure and compensatory changes in outflow facility.

In the diagnosis of glaucoma, flattening of the tonographic tracing has been a most characteristic finding.|| The fact that impaired outflow can exist in the absence of elevated intraocular pressure has emphasized the role of tonography in the early diagnosis of glaucoma. The decreased facility in open angle glaucoma as well as in most other types of glaucoma has been confirmed by many observers.¶ The common pitfalls and instrumental difficulties in tonography have been discussed in very practical and useful fashions for the beginner.#

Eyes with glaucoma and retinal vein occlusion have been reviewed,* with emphasis placed on the findings of Verhoeff [622] that preexisting glaucoma pre-

¶ Becker, B., and Friedenwald, J. S.: Unpublished data.

References 5 and 274. Kronfeld, P. C.: Exhibition of the Committee on Standardization of Tonometers, presented at the XVII International Congress of Ophthalmology, New York, Sept. 10-17, 1954.

* References 260, 262, 368, and 653.

† References 25 and 107.

‡ Reference 191; Becker, B.: Unpublished data.

§ References 267 and 568.

|| References 266 and 456.

¶ References 75, 106, 132, 183, 191, 256, 258, 362, 368, 505, 532, 567, 568, 572, and 614.

References 34 and 568.

* References 560 and 561.

disposes to occlusion of the central retinal vein. This important fact is overlooked frequently.[640] It is so common an experience in a tonography laboratory to find evidence of impaired outflow in the contralateral eye of patients presenting with central vein occlusion, with or without hemorrhagic glaucoma, that students are now taught to rule out primary glaucoma in all vein occlusions. This diagnosis is of particular importance; for it often permits earlier therapy of chronic simple glaucoma in an essentially one-eyed patient.

There has been increasing evidence that provocative tests combined with tonography permit the earlier recognition of glaucoma than does either alone. Pupillary dilatation in patients with closed angle glaucoma and water-drinking in those with chronic simple glaucoma produce two types of changes: an increase in intraocular pressure and a decrease in facility of outflow.† However, several laboratories have failed to note a consistent decrease in facility of outflow following water-drinking.‡

Factors such as the ratio P_o/C have been used in order to take into account both the alterations in intraocular pressure (P_o) and facility of outflow (C).§ This has led to a much sharper differentiation between normal eyes and eyes with established chronic simple glaucoma. Thus, a series of patients with chronic simple glaucoma, proved by characteristic loss of visual field, were subjected to water-drinking provocative tests while on no therapy. Repeat tonography revealed that only 53 (28%) of the 188 eyes had a pressure rise of 8 mm. Hg or more after the consumption of 1 liter of water.[69] A similar incidence of water-drinking tests has been reported in a larger series of glaucomatous eyes.[400] However, following water-drinking, 182 (97%) of the same series of 188 eyes with untreated chronic simple glaucoma presented a value for P_o/C of 100 or more. Only 2 eyes (1%) of a group of 175 normal eyes were found to have such elevated values for this ratio after water. It is hoped that this method of interpretating tonograms will permit the earlier diagnosis of glaucoma. There are indications that this has proved true [309] not only for the diagnosis but also for the evaluation of the therapy of the glaucomas.

(*b*) Evaluation of Therapy: Pilocarpine and eserine increase outflow facility in both normal and glaucomatous eyes and thus lower intraocular pressure.‖ Failure of these therapeutic measures has been preceded and predicted often by a progressive decline in outflow facility in spite of insignificant or only intermittent rises in intraocular pressure.¶ Statistical data should become available soon proving the significance of such tonographic changes, but it is already apparent that eyes with low facility should be checked much more frequently as to status of visual field and probably should be treated more intensively.#

The use of topical BC 48 (decamethylene-bis[N-methyl-carbaminoyl-*m*-trimethyl-ammonium-phenol]) has been described [250] as a miotic in the therapy of glaucoma. It was found to have many of the properties of isoflurophate (DFP), but was water-soluble and stable. Pyridostigmine (5%) was noted to have about the same effect as 1% prostigmine.[302]

† References 34, 69, 75, and 579.
‡ References 181, 532, and 583.
§ Reference 69; Leydhecker, W.: Personal communication to the author, 1956.
‖ References 60, 645, and 653.
¶ References 34, 60, and 75.
# References 34 and 75.

There appears to be little question that successful filtering procedures, such as iridencleisis, trephination, or anterior sclerectomy, result in large increases in outflow facility.* Thus, the obstructed outflow truly is by-passed in these eyes. Evidence continues to accumulate that the failure of filtering blebs is associated with, and often is preceded by, a flattening of the tonographic tracing.†

Cyclodialysis appears to improve outflow facility in aphakic glaucoma and in some eyes with chronic simple glaucoma for a variable time interval. However, the decreased production of aqueous that follows this procedure can maintain hypotension for prolonged periods.‡ The possibilities of performing a cyclodialysis through a goniotomy incision have been demonstrated.[52] This new approach to the surgical therapy of glaucoma may also help to unravel the mode of action of detaching the ciliary body and establishing a communication between the anterior chamber and the suprachoroidal space.

Goniotomy is believed to permit access of aqueous to Schlemnn's canal.§ Although the value of goniotomy in the therapy of congenital glaucoma has been well established, available tonographic data are incomplete and conflicting as to its mode of action. Some eyes demonstrate an improvement in facility following goniotomy, whereas a profound decrease in production of aqueous appears to dominate the postoperative course in other instances of congenital glaucoma after successful goniotomy.‖ More tonographic data on the preoperative and postoperative course of congenital glaucoma are badly needed. These measurements must take into account the effects of anesthesia as well as deviations from normal values for corneal curvature and scleral rigidity.

The usefulness of the facility of outflow in deciding whether to do a peripheral iridectomy or iridencleisis in closed angle glaucoma has proved its reliability repeatedly.[66] Thus, no matter how dense the synechiae, how many attacks, or how long the eye has been in an attack, an adequate outflow facility has suggested a peripheral iridectomy as the surgical procedure of choice. On the other hand, obstruction to outflow, as evidenced by a persistently flat tonographic curve, in spite of miotic therapy, has required such filtering operations as iridencleisis. This has appeared to hold true whether the obstruction to outflow was visible, in the form of peripheral anterior synechiae, or related to primary or secondary trabecular damage.

Confirming the findings of previous observers,¶ several reports have appeared on the excellent results and relative innocuousness of peripheral iridectomy in closed angle glaucoma.# A study [660] of the histories of patients with closed angle glaucoma revealed an incidence of acute glaucoma in 89% of the fellow eyes when untreated or intermittently treated with miotics. Even in those patients who used miotics continuously, 40% developed acute glaucoma in the fellow eye. These figures provide a strong argument for prophylactic surgery in closed angle glaucoma. Most exciting are the possibilities of using the photocoagulation method [445] to produce peripheral iridectomies without operative incision.[446] This avoids the possibilities of anterior synechiae from loss of the anterior chamber. The removal

* References 60, 268, and 640.
† References 34, 60, and 75.
‡ References 259, 370, and 640.
§ References 48 and 50.
‖ Becker, B.: Unpublished data.
¶ References 47, 51, 135, and 291.
# References 428, 463, and 573.

of only anterior layers of the iris in attempting peripheral iridectomy for closed angle glaucoma has been described again.[287] This resulted in a herniation forward of the pigment epithelium and failure to widen the angle. Such findings provide additional evidence for a higher pressure in the posterior chamber than in the anterior chamber and confirm the mechanism of the function of peripheral iridectomy in this disease process.

A number of papers have appeared on improved techniques for filtering procedures and their sequelae,* as well as evaluations of the results obtained in surgical series.† The use of gelatin film in glaucoma surgery has been described.[386] Subconjunctival cortisone has been found to have no significant effect on the success of filtering operations.[295]

A series of surgically treated eyes with open angle glaucoma were observed to lose more field than a comparable group of eyes medically treated.[110] It has been pointed out that chronic simple glaucoma may run a self-limited course.[420] These reports as well as the complications of surgery raise interesting questions as to a reevaluation of indications for surgery in this type of glaucoma.

A self-limited course has been noted ‡ in a series of glaucomatous eyes with impaired outflow. These eyes had a history of elevated intraocular pressure but subsequent spontaneous hyposecretion of aqueous and normalization of intraocular pressure in spite of persistence of the decreased outflow facility. In some instances these eyes lost field during their hypertensive phase of glaucoma and then failed to lose further field when intraocular pressure was normalized. Thus, partial secretory failure accounts for the self-limited or compensated nature of the disease in these eyes and is consistent with the blunting and atrophy of the ciliary processes seen in such long-standing chronic simple glaucoma. The role of some types of surgery in hastening this process of secretory failure in the ciliary body needs evaluation. The long-term use of agents which decrease the rate of aqueous flow § is based upon this same emphasis on the importance of maintaining intraocular pressure at normal levels in spite of impaired outflow function. The fact that such eyes can be maintained successfully without field loss if intraocular pressure is normalized provides additional evidence for this thesis.

An enormous clinical experience with tonography has been accumulated in several large glaucoma centers. In the near future this should permit the correlation and interpretation of results of this procedure with other changes of glaucoma and with its subsequent clinical course. Such initial tentative conclusions as the ability to diagnose open angle glaucoma in a phase of decreased secretion, the value of tonography used in conjunction with provocative tests in the early diagnosis of glaucoma, and the evaluation of type and adequacy of glaucoma therapy are attractive and provocative. They have proved useful as working hypotheses, but they need statistical confirmation. It is apparent that much more basic data ‖ are needed on the correlation between low facility of outflow and

* References 55, 58, 89, 139, 159, 231, 245, 313, 356, 391, 424, 427, 429, 461, 510, 521, 522, 523, 533, 569, 606, 617, 630, and 633.

† References 84, 85, 94, 99, 133, 138, 168, 170, 173, 187, 192, 204, 211, 301, 310, 330, 332, 338, 341, 344, 435, 443, 458, 469, 471, 475, 504, 512, 515, 528, 546-549, 558, 565, 607, 621, 626, 630, 632, and 652.

‡ Becker, B.: Unpublished data.

§ References 77, 375, 393, and 605.

‖ References 267 and 369.

other characteristics of chronic simple glaucoma. It is only in this fashion that the true value of this laboratory test will become established.

II. Rate of Formation of Aqueous Humor (*F*)

Measurement of rate of aqueous flow has been achieved by two entirely independent approaches, each with its own uncertainties and sources of error. The over-all agreement of values obtained by different methods and in several laboratories has been most satisfying. It is likely either that the estimates are close to the truth and various assumptions made are reasonably valid or that the errors tend to compensate for one another and the agreement is pure chance. I favor the more optimistic former view, at least as a working hypothesis until more data are available.

A. Theory and Measurement

The rate of aqueous flow has been estimated from measurements of facility of outflow by tonography or perfusion by means of Equation (1) discussed in Part I of this review. The tonographic approach has been of great practical value in measurements on human eyes as well as very useful in the laboratory for rabbit eyes. Repeated measurements have been made on the same eye rather than to assume identical values for both eyes. Although subject to many instrumental, physiologic, and theoretical sources of error, many of the inaccuracies inherent in tonography are avoided when it is used for measuring relative changes in rate of flow rather than absolute values.

The turnover rate in the aqueous humor of systemically administered test substances has provided the basis for most other means of measuring the rate of formation of aqueous humor. The only one of these compounds applied thus far to human eyes has been fluorescein.¶ Unfortunately, the sources of error in this method as well as the technical difficulties encountered in carrying out the procedure have limited its use.# With the availability of posterior chamber as well as anterior chamber data in rabbits,[347] more precise formulations [352] and a general mathematical theory [242] of aqueous humor dynamics have been presented. Various assumptions made and sources of error have been analyzed in detail in the latter paper. Practical demonstrations of the application of the theory to thiocyanate, sodium, and ascorbate turnover data have been presented.

From turnover studies in the posterior and anterior chamber aqueous humor of rabbit eyes, using thiocyanate or sodium as a test substance, the rate of flow has been estimated at approximately 1.7% of the capacity of the anterior chamber per minute.[352] Corrections suggested [163] for protein binding of thiocyanate would reduce these estimates to approximately 1.4% per minute.

The *p*-aminohippuric acid method [43] has been improved [45] for the determination of the rate of aqueous flow, and average values of 1.1% per minute were found for Swedish rabbit eyes. Questions have been raised, however, as to whether *p*-aminohippuric acid may itself alter aqueous flow.* Thus, tonographic evidence is available that *p*-aminohippuric acid may decrease aqueous flow in rabbits by some 20% to 30%.† With the smaller amounts of *p*-aminohippuric acid used in

¶ References 257 and 262.

References 75 and 239.

* Friedenwald, J. S.: Recent Studies on Aqueous Flow, read before the Wilmer Residents Association Meeting, Baltimore, April 2, 1954.

† Reference 387; Constant, M. A.: Unpublished data.

the modified method, however, such decreases in aqueous flow are probably of lesser magnitude. The *p*-aminohippuric acid method has been further criticized on the basis of its failure to evaluate posterior chamber data and the "reservoir" factor.‡ The revised *p*-aminohippuric acid method,[43] however, is one of the most convenient and useful of the chemical methods available for measuring flow. Unfortunately, as in so many of the chemical methods, it depends upon both eyes of the animal behaving in identical fashion. There is ample evidence from tonographic tracings to demonstrate that this is frequently not a valid assumption. An ingenious suggestion for using multiple isotopic test substances injected at predetermined time intervals permits obtaining time-concentration curves from single sampling.[411] This method should provide a means of avoiding spontaneous differences between eyes as well as the effects on the contralateral eye of withdrawing aqueous.

Estimates of aqueous flow in rabbit eyes, using ascorbic acid as a test substance, were interpreted as indicating a rate of flow of 1.7% to 1.8% of the anterior chamber per minute.[65] This value may be significantly higher than that reported for sodium or thiocyanate and raises the question as to whether saturation with ascorbic acid increases the rate of formation of aqueous humor. The change in steady-state concentration of ascorbate after plasma levels of ascorbic acid are raised also suggests some 25% to 30% increase in coefficient of flow (assuming no change in the diffusion coefficient). However, increases of flow of such magnitude in rabbit eyes have not been confirmed by tonography,§ fluorescein appearance time,[377] or bicarbonate changes.‖ The decreased rate of secretion suggested for scorbutic guinea pigs ¶ has not been confirmed by recent turnover or steady-state determinations.# Further studies in progress on rabbit and guinea pig eyes should help to clarify these findings.

A review of all the available turnover data reveals that some 2.5 to 3.5 cu. mm. per minute flow through the rabbit eye. These values are in reasonable agreement with average tonographic data for rabbits (3.0 to 3.5 cu. mm. per minute).*

With increased emphasis on means for altering rate of aqueous formation in patients and experimental animals, various simplified methods and short cuts have been applied in attempts to quantitate the effects obtained. Most of these are of particular value and less subject to error when used to measure relative flow rates or per cent changes in rate of aqueous formation. Thus, the appearance time of fluorescein through the pupil after intravenous injection[550] has been revived as a rough relative determination of the rate of aqueous flow in rabbit, human, and dog eyes.† This method depends upon fluorescein entering the eye primarily through the posterior chamber. This has been proved for rabbits by

‡ Friedenwald, J. S.: Personal communication to the author.

§ Becker, B., and Constant, M. A.: Unpublished data.

‖ Becker, B., and Constant, M. A.: Unpublished data.

¶ References 243 and 541.

References 39 and 507.

* References 67, 70, and 365.

† References 60 and 384. Demorest, B. H., and Becker, B.: Unpublished data; Linnér, E., and Friedenwald, J. S.: Recent Studies on Aqueous Flow, read before the Wilmer Residents Association Meeting, Baltimore, April 2, 1954.

posterior chamber analysis.‡ It also assumes that flow from posterior to anterior chamber is essentially linear and that no changes in permeability to fluorescein are induced by the method of altering flow. These assumptions have proved reasonably valid in some applications of the method but entirely unreliable in others.

The change in steady-state concentration of normal substances in the posterior and anterior chambers of rabbit eyes can be used as a measure of the alteration in rate of flow. This method is based on the derivation of the ratio of the flow coefficient (K_F) to the diffusion constant (K_D) from measurements of posterior chamber, anterior chamber, and plasma concentrations of the substance.[352] It provides a useful and relatively simple method for evaluating alterations in the ratio K_F/K_D. However, as a measure of flow, this technique is only valid if the diffusion coefficient for the particular substance studied has not been changed in the process of varying the rate of secretion. Since it necessitates using one eye before and the other eye after the induced change, this approach also assumes that both eyes have similar values at the onset. It also requires a lack of effect on the contralateral eye of withdrawing fluid from the posterior and anterior chamber of the control eye. In the rabbit eye ascorbic acid and bicarbonate prove most useful for this type of measurement because of their ease of determination and the considerable differences found in anterior chamber, posterior chamber, and plasma values. Such relative measurements have been applied to studies of the effects on aqueous flow of carotid ligation,[365] acid burns of the cornea,[285] and carbonic anhydrase inhibition.[63]

B. Alterations in Rate of Aqueous Formation

1. *Spontaneous Variations.*—From repeated tonographic tracings on normal and glaucomatous human eyes, it has been concluded that the phasic diurnal variations in intraocular pressure are dependent upon changes in rate of aqueous formation.[181] These findings have been confirmed, and it has been pointed out that eyes with impaired outflow facility demonstrate greater fluctuations in intraocular pressure for a given change in secretion than do normal eyes.[274] Ganglionic blocking agents,§ as well as stellate ganglion block,[155] have been described as decreasing such diurnal fluctuations in secretion. However, it has been denied that this is the mechanism of diurnal changes and claimed that such variations are related to alterations in outflow facility[316] or vasomotor effects[199] (see Part III). As Friedenwald has pointed out,[238] if vasomotor effects induce alterations in flow, the divergence of views may be reconciled.

The ocular hypotension associated with retinal detachments, with some instances of uveitis, and with phthisis bulbi has been found to result from failure of the secretory process.[642]

The spontaneous, intermittent, or prolonged hyposecretion exhibited by patients with glaucoma and obstructed outflow has been commented upon above. This factor may be much more prevalent in the population than has been appreciated in

‡ Reference 384. Demorest, B. H., and Becker, B.: Unpublished data; Linner, E., and Friedenwald, J. S.: Recent Studies on Aqueous Flow, read before the Wilmer Residents Association Meeting, Baltimore, April 2, 1954.

§ Rosen, D. A.: The Effects of a Ganglionic Blocking Drug, Pentapyrrolidinium, on Ocular Fluid Dynamics: A Preliminary Report, read before the East Central Section of the Association for Research in Ophthalmology, Toronto, Canada, Jan. 9, 1955.

the past. It may well be that many eyes with potential glaucoma fail to develop overt manifestations of pressure rise or field loss because of the phenomenon of hyposecretion. This may also account for some instances of spontaneous arrests reported in chronic simple glaucoma.[420]

Persistent or intermittent hypersecretion as a means of raising intraocular pressure to glaucomatous levels in the absence of impaired outflow facility has been noted as a rare form of chronic simple glaucoma.‖ It has been necessary to differentiate the findings of an elevated intraocular pressure with a normal or high normal facility of outflow from the similar uncorrected tonographic tracing seen in a normal or glaucomatous eye with increased scleral rigidity. Many eyes presenting this set of findings had been considered nonglaucomatous until recent evidence became available that such eyes have lost visual field in a fashion characteristic of glaucoma.[76]

The mechanism or stimulus to alterations in secretion remains unknown, but there is suggestive evidence that it may originate centrally.¶ The frequent association of neurogenic hypertension and hypersecretion glaucoma also points toward a diencephalic origin of this phenomenon. However, even in the type of glaucoma dependent upon hypersecretion and suggestive of a neurovascular mechanism, the loss of field tends to be related to the degree and persistence of the intraocular pressure elevation.

The spontaneous initiation of secretion has been offered as an explanation for the rise in ascorbic acid levels in the aqueous humor of human eyes between the sixth and ninth fetal months,# as well as the sudden increase in intraocular pressure of prematures to normal values at the approximate fetal age of 200 days.[116] In rabbits, ascorbate concentrations of the aqueous humor reached adult levels at 27 days of age, and in the monkey, at 5 months after birth.* Intraocular pressure measurements in these animals would be of interest.

2. *Carbonic Anhydrase Inhibition and Aqueous Flow.*—Carbonic anhydrase was first described in rabbit ciliary body-iris preparations by Wistrand.[661] This finding and the excess of bicarbonate noted in rabbit aqueous,† as well as the need for bicarbonate buffering in the ciliary body postulated in the theory of Friedenwald,[233] suggested a role for carbonic anhydrase in the formation of aqueous humor.

When sulfanilamide was found to inhibit carbonic anhydrase, unsuccessful attempts were made to alter intraocular pressure in rabbits with the drug.‡ The synthesis of sulfonamide derivatives with more potent qualities of carbonic anhydrase inhibition § and their extensive pharmacologic investigation ‖ have made available a number of compounds for clinical and experimental trial. Almost all potent carbonic anhydrase inhibitors tested have been found to lower intraocular pressure in experimental rabbits, guinea pigs, dogs, and cats.¶ Acetazoleamide was selected for clinical trial because of its comprehensive phar-

‖ References 24, 34, 75, 76, 132, and 191.
¶ References 125, 423, 454, 497, 498, 529, 539, 540, 570, 571, and 628.
# References 350 and 351.
* References 350 and 351.
† References 347 and 367.
‡ Kinsey, V. E.: Personal communication to the author.
§ References 449 and 513.
‖ References 431 and 433.
¶ References 62, 251, 252, 254, 272, 348, and 537.

macologic investigation, its extensive use in patients as a diuretic agent, and its remarkable margin of safety. The ability of this agent to lower intraocular pressure in human eyes[61] has led to its widespread clinical acceptance. The availability of means for altering rate of aqueous flow has also stimulated considerable thought and energy among investigators interested in chemical composition and dynamics of the aqueous humor.

The recent evidence presented of a deficit of bicarbonate in one human eye[165] raises a most intriguing question as to the application of results of rabbit aqueous chemistry studies to human eyes. An excess of chloride in dog aqueous humor was previously reported.[167] Excesses of chloride were also noted in rabbit[303] and human # aqueous humor. These findings were reviewed by Kinsey and proved to depend upon the method used for the determination of chloride in plasma.[345] When more accurate methods were used, no excess of chloride was found in aqueous humor from human eyes and deficits of chloride were observed in dog and rabbit eyes. Direct determinations of bicarbonate in dog eyes have revealed a 4 mM. excess in aqueous humor as compared with plasma,* thus justifying Kinsey's conclusions.[345] The excess of bicarbonate in animals responding to acetazoleamide (dog, cat, guinea pig, and rabbit) suggests a similar excess in the human eye. However, bicarbonate concentrations in the aqueous may be only incidental to the effects of carbonic anhydrase inhibition. Only direct bicarbonate measurement on a number of normal and glaucomatous human eyes will clarify this point. Such bicarbonate concentrations in human eyes, both before and after acetazoleamide administration, need further exploration. It would also be of interest to study the effect of carbonic anhydrase inhibition on aqueous flow and composition in the horse, goat, and monkey eye, where the greatest deficiency of carbon dioxide content was observed.† In this regard, one must recall that the usual effects of carbonic anhydrase inhibition on the mammalian renal tubule have resulted in a decreased reabsorption of bicarbonate, water, and sodium.‡ In the alligator, however, acetazoleamide administration led to a decreased reabsorption of chloride and increased reabsorption of bicarbonate.§ Furthermore, carbonic anhydrase inhibition has been observed to decrease the acid formation of the gastric mucosa || as well as the alkaline secretion of the pancreas.[98]

(*a*) Effects of Carbonic Anhydrase Inhibitors on Composition and Rate of Formation of Aqueous Humor: Acetazoleamide induced a profound fall in posterior chamber and anterior chamber bicarbonate concentrations in rabbits and guinea pigs, reducing the excess over plasma concentrations.[63] Several observers have confirmed these changes in bicarbonate concentrations as well as pH alterations in the anterior chamber fluids of rabbits after acetazoleamide.¶ The failure to find significant changes in aqueous bicarbonate in one set of experiments[278] has been explained on the basis of not measuring posterior chamber concentrations and studying the anterior chamber fluids at too short an interval after the administration of acetazoleamide.# The fact that posterior chamber bicarbonate

References 311 and 503.
* References 164 and 165.
† References 164 and 165.
‡ References 432 and 434.
§ References 150 and 306.
|| References 160 and 329.
¶ References 29, 109, 209, 348, 378, 380, 389, and 657.
# References 63 and 237.

concentrations fall in spite of the decrease in secretion indicates that production of bicarbonate is more markedly inhibited than the secretion of water. These findings support an indirect rather than a direct role of bicarbonate in the formation of aqueous humor.

A rise in posterior chamber and anterior chamber ascorbic acid has been noted following acetazoleamide administration to normal and nephrectomized rabbits.* This occurred both at low plasma ascorbic acid levels and at artificially elevated plasma levels.† Expected increases in aqueous chloride of rabbit eyes have been noted after acetazoleamide administration.[348] Striking increases in the excess over plasma of aqueous lactate levels were observed following carbonic anhydrase inhibition.[73] These findings are consistent with the thesis of lactate production by the lens and other intraocular structures. The increased concentrations would result from the partial stagnation of aqueous consequent upon the decreased rate of flow. In dogs, acetazoleamide has been found to reduce the conductivity of the aqueous humor.‡ A fall in rabbit aqueous potassium concentration after acetazoleamide administration has been reported.§

Assuming no change in the diffusion constant (and this has been proved for ascorbic acid by analysis of turnover data), the change in steady-state concentrations of bicarbonate and ascorbate in the posterior chamber and anterior chamber of rabbit eyes was consistent with an average suppression of aqueous flow of 50% to 60%.[63]

All available tonographic evidence, both in rabbits and in humans, indicates that acetazoleamide induces a reversible lowering of intraocular pressure without improving facility of outflow.‖ Tonographic findings are consistent with a decreased formation of aqueous humor, averaging some 50% to 65%. Failure of some observers[277] to obtain large falls in intraocular pressure in rabbits has been demonstrated to represent compensatory decreases in facility of outflow so as to maintain intraocular pressure in spite of very similar magnitudes of partial suppression of aqueous flow.[70] This is in excellent agreement with the lack of significant differences in carbonic anhydrase activity or acetazoleamide concentration in the ciliary processes between the animal with maximal and one with minimal pressure responses.[36]

The suppression of aqueous flow as the mechanism of action of acetazoleamide has not been uniformly accepted. For example, it has been postulated that the dehydration of the sclera following acetazoleamide administration results in a decrease in the resistance to outflow from the anterior chamber and a fall in intraocular pressure.¶ This concept is based upon the theory of edema of the sclera as the mechanism and site of obstruction in glaucomatous eyes (see above) and the lack of effect of acetazoleamide administration on the appearance of the aqueous veins. A failure to alter the rate of turnover of sodium in the anterior chamber by acetazoleamide has also been offered as evidence of a lack of effect upon aqueous secretion.[305] However, this thesis is not supported by, nor consistent with, other turnover and tonographic data.

An increased reabsorption of aqueous by the ciliary body has been postulated

* References 63 and 348.
† References 63 and 381.
‡ References 612 and 613.
§ References 210 and 586.
‖ References 2, 61, 62, 272, and 651.
¶ References 354 and 357.

to follow acetazoleamide administration.# Altered permeability in the rabbit eye after oral acetazoleamide has been noted.[15] However, neither of these concepts has received general acceptance or confirmation.

The appearance time of fluorescein is increased in both rabbit and human eyes following the administration of acetazoleamide.* The changes induced in unanesthetized rabbits and patients were consistent with an estimate of some 45% to 55% inhibition of rate of flow. Using the *p*-aminohippuric acid method, similarly decreased aqueous flow rate in rabbits has been reported following acetazoleamide.[343] Turnover studies, using ascorbic acid as a test substance, have been analyzed both by exponential analysis of anterior chamber data and linear analysis of posterior and anterior chamber data. They revealed a change in rate of aqueous production in rabbit eyes from an average normal of 3.5 cu. mm. per minute to an acetazoleamide-treated value of 1.7 cu. mm. per minute, or some 50% suppression.[65]

It is apparent that various methods of measuring changes in aqueous flow have been in reasonable agreement as to the degree of suppression induced by carbonic anhydrase inhibition in both rabbit and human eyes (50% to 60%).[67] Comparison of two independent methods on the same animal (e. g., tonography and steady-state bicarbonate) has provided even closer agreement.[70] It has also been established that enormous increases in the dose of acetazoleamide have failed to suppress flow beyond this amount. This has been explained on the basis of the uncatalyzed hydration and dehydration of carbon dioxide occurring sufficiently rapidly to support some 40% to 50% of normal flow. Additional evidence for this concept has been obtained by the administration of acetazoleamide to patients with rate of aqueous formation spontaneously reduced to less than 1 cu. mm. per minute. Under these circumstances, there was very little fall in intraocular pressure or rate of secretion of the aqueous following carbonic anhydrase inhibition.[60] Similarly, a trend toward less scatter of flow rates was observed in patients receiving acetazoleamide therapy.[375] Clinically, the uncatalyzed residual rate of secretion has limited the therapeutic effectiveness of acetazoleamide in lowering intraocular pressure. However, the persistent residual flow may well have been an important protective factor in preventing ocular toxicity even at excessive doses of acetazoleamide.

(*b*) Site of Action of Acetazoleamide: The original finding of carbonic anhydrase in the ciliary body of rabbit eyes[601] has been verified,† and its location has proved to be in the dissected ciliary processes.[36] Furthermore, acetazoleamide has been demonstrated to inhibit the carbonic anhydrase of the ciliary processes.‡ These findings and the effect of carbonic anhydrase inhibition on secretion of the aqueous strongly suggest that acetazoleamide acts directly on the enzyme in the ciliary body.§ There is need, however, for measurements of the carbonic anhydrase content of the ciliary processes in human eyes and the effects of acetazoleamide on the enzyme in this site.

References 654 and 657.

* References 60, 67, 378, and 380. Demorest, B. H., and Becker, B.: Unpublished data; Linnér, E., and Friedenwald, J. S.: Recent Studies on Aqueous Flow, read before the Wilmer Residents Association Meeting, Baltimore, April 2, 1954.

† References 253, 279, and 281.

‡ References 36, 171, and 279.

§ References 62 and 91.

A delay in fluorescein appearance time and lowering of bicarbonate excess over the depressed plasma concentrations has been recorded following ammonium chloride administration.[382] Therefore, the interesting question was raised as to whether the acetazoleamide effect was merely one of systemic acidosis and not associated with an inhibitory action on the carbonic anhydrase activity of the eye. It has also been postulated that the ocular effects of acetazoleamide are secondary to the diuresis and systemic changes in blood sodium.|| This hypothesis is based upon a similar time of onset of the ocular hypotension, diuresis, and alterations in serum electrolytes after oral administration of acetazoleamide.

However, it would appear to be unlikely that the ocular hypotensive effect of carbonic anhydrase inhibitors is dependent upon their renal action or that systemic acidosis is the entire explanation for the effects on intraocular pressure. The rapidity of the action of acetazoleamide upon the eye after intravenous administration ¶ suggests a direct action on the ciliary body. Also, similar falls in aqueous bicarbonate and intraocular pressure can be obtained in acetazoleamide-treated animals which demonstrate no decrease in plasma bicarbonate levels.[63] The cessation of diuresis observed and the normal electrolytes found during long-term carbonic anhydrase inhibition have not interfered with effective suppression of aqueous flow. Furthermore, other diuretic agents, such as mercurial or xanthine derivatives, produce no consistent lowering of intraocular pressure in spite of loss of sodium. Most significantly, identical falls in rate of secretion, intraocular pressure, and aqueous bicarbonate concentrations are seen in nephrectomized rabbits and guinea pigs where the renal induced electrolyte changes and loss of bicarbonate are avoided.# It is also true that the renal action of acetazoleamide can be blocked by ammonium chloride administration.[432] Even such ammonium chloride pretreated, acidotic animals demonstrate further falls in intraocular pressure and aqueous bicarbonate concentration after administration of acetazoleamide.[62] On the other hand, ammonium chloride administration to patients appears to potentiate the effects of acetazoleamide on intraocular pressure.[64] Furthermore, severely acidotic patients (e. g., in diabetic coma) demonstrate marked ocular hypotension and osmotic factors can alter rate of aqueous secretion (e. g., intravenous sorbitol—see below). Thus, although systemic acidosis does not seem essential for the action of acetazoleamide on the human eyes, dehydration or severe acidosis is capable of contributing to the lowering of intraocular pressure. The contribution of systemic changes to the ocular hypotensive effects of acetazoleamide under clinical circumstances needs further study, but it would appear unlikely that these play a primary role in the mechanism of action of carbonic anhydrase inhibitors on the eye.

The failure of acetazoleamide and other carbonic anhydrase inhibitors to act upon intraocular pressure or lower aqueous bicarbonate when applied topically or subconjunctivally * is not only unfortunate from the clinical point of view but also prevents the establishment of the locus of action. Explanations such as failure of penetration of drug in vivo to a critical enzyme site (e. g., stroma of the ciliary body) have been offered.† The failure to act locally cannot be ex-

|| References 127 and 129.
¶ References 62, 254, and 662.
# References 62, 91, and 662.
* References 62, 91, 114, 216, 251, 254, 272, 277, and 280.
† References 62, 237, and 280.

plained on the basis of a lack of associated systemic acidosis; for animals made acidotic with ammonium chloride still fail to obtain suppression of aqueous flow following local administration of acetazoleamide.‡ The findings that the blood and urine of acetazoleamide-treated patients or animals will not lower intraocular pressure when applied topically tend to rule out the role of an alteration in the drug during its passage through the organism so as to become effective in its action on the ciliary body.§ On the other hand, would one anticipate that topical administration to the kidney would induce a diuresis? At any rate, the failure of local administration to the eye remains a thorny, but unsolved, problem of theoretical as well as practical importance.

It has been proposed that carbonic anhydrase may play an important role in maintaining the efficacy of the bicarbonate buffer in such secretory cells as those of the gastric mucosa or renal tubules.[161] Under these circumstances, carbonic anhydrase is more critically needed the greater the rate of secretion and tendency for pH of the secretory cell to change. Thus, if the primary secretory product is the cation sodium || or, more probably, an exchange of sodium for hydrogen in the ciliary epithelium (analogous to that postulated for the renal tubule),¶ these cells would accumulate an excess of hydrogen ions and undergo a fall in pH. The availability of adequate bicarbonate buffering would be necessary for the cells to continue such a process, and carbonic anhydrase of the cell might then be the critical factor in the over-all rate of secretion.

Similar reasoning has been applied to the electron transport theory of aqueous secretion.[236] This theory postulates the formation of hydroxyl ions in the epithelium and their transfer into the aqueous humor. Under such circumstances, bicarbonate buffering capacity would be necessary to compensate for stromal acidosis or epithelial alkalosis of the ciliary body, whichever be the limiting factor in secretion. The potentiation by ammonium chloride of the acetazoleamide effect on aqueous flow under clinical circumstances suggests an acidotic stroma as the critical defect. However, an intensification of the acidosis of the secretory cell exchanging sodium for hydrogen would also explain the ammonium chloride effect. It is of considerable interest that sodium chloride administration also potentiates the anticonvulsant action of acetazoleamide # but blocks the renal effect.[432]

One may thus attempt to summarize the data on site and mechanism of action of acetazoleamide on intraocular pressure as a partial suppression of aqueous humor formation, probably resulting from the inhibition of carbonic anhydrase of the ciliary processes.* The details of how carbonic anhydrase inhibitors alter secretion are still not resolved and are dependent for their solution on a thorough understanding of the secretory process itself. An acceptable hypothesis at present can be formulated in terms of the local inhibition of carbonic anhydrase (with or without systemic respiratory and renal alterations in carbon dioxide content and pH) impairing the buffering capacity of the secretory organ.

(*c*) Clinical Uses of Acetazoleamide in the Glaucomas: The short-term administration of acetazoleamide in acute closed angle glaucoma as well as in self-

‡ Becker, B.: Unpublished data.
§ Becker, B.: Unpublished data.
|| References 162 and 166.
¶ References 93 and 511.
# References 450 and 451.
* References 62 and 91.

limited secondary glaucoma has received widespread acceptance, and there is general agreement as to its usefulness.† Oral doses of 250 to 500 mg. every four to six hours have been generally used, and many ophthalmologists have used 250 mg. in 5 cc. of water for injection intravenously or intramuscularly for more rapid effect or in vomiting patients. The parenteral injections have been repeated in two to four hours, and oral medication has been begun or continued. Acetazoleamide has also been used successfully as preoperative medication in all types of glaucoma, including congenital glaucoma, closed angle glaucoma, chronic simple glaucoma, glaucoma and cataracts, hemorrhagic glaucoma, and traumatic glaucoma. The lowering of intraocular pressure obtained by the administration of acetazoleamide has often permitted sufficient clearing of corneal edema and time for more adequate examination. Thus, views of the angle and fundus and evaluation of fields and vision became possible. The findings noted have frequently altered the prognosis or aspects of the treatment of the particular eye. Delaying surgery and continuing acetazoleamide administration has often permitted operation on a less inflamed eye with less danger and more chance for successful filtering procedures. The finding of areas of nonoccluded angle by gonioscopy or adequate facility of outflow by tonography has allowed the use of peripheral iridectomy instead of iridencleisis in the closed angle group of glaucomas.

It has been emphasized repeatedly that partial suppression of outflow of aqueous by acetazoleamide did not interfere with measures designed to improve the impaired outflow system. Thus, local miotics in primary glaucoma or local mydriatics and cortisone in iritis with secondary glaucoma have been applied as indicated. In fact, it has been demonstrated that the pressure-lowering effect of systemic carbonic anhydrase inhibition and topical pilocarpine were truly additive in some instances of chronic simple glaucoma.[60] Often, the effects of acetazoleamide on intraocular pressure have been potentiated by the addition of ammonium chloride in doses of 1 gm. every four to six hours.[64]

As an example of the effectiveness of acetazoleamide therapy, a decrease in flow of over 40% was observed in 320 (84%) of a series of 380 consecutive eyes seen in the Washington University Clinics.[64] Only 25 eyes (7%) failed to obtain 20% inhibition of secretion. Results in 60 normal eyes indicated much the same responsiveness to acetazoleamide as measured by induced changes in rate of secretion of aqueous. Almost identical results were recorded at the Wills Eye Hospital,[392] where 344 (85%) of 406 glaucomatous eyes sustained a pressure fall of some 10 mm. Hg. Other series reported have been in essential agreement with these findings. As anticipated, pressure falls in millimeters of Hg were less dramatic in eyes with lower intraocular pressure.

It has been a common experience in most series that hemorrhagic glaucoma responds poorly to carbonic anhydrase inhibition or responds for a time and then fails to respond. The reasons for the poor results in such eyes remain unexplained. Serious side-effects of acetazoleamide have not been a prominent feature of short-term acetazoleamide administration, but most patients experience paresthesias.

† References 2, 13, 14, 19, 20, 57, 59, 61, 64, 79, 90, 91, 114, 177, 193, 207, 208, 272, 314, 336, 354, 394, 395, 402, 422, 430, 455, 460, 476, 482, 495, 508, 551, 556, 566, 611, 621, 624, 650, 651, and 654. Thorpe, H. E.: Carbonic Anhydrase Inhibitor as a Therapeutic Agent in Ophthalmology, read before the Association for Research in Ophthalmology, Eastern Division, Philadelphia, Feb. 18, 1954.

Acetazoleamide has also been used successfully in the therapy of some eyes with postoperative flat anterior chambers,‡ in endothelial corneal dystrophy with corneal edema,§ and in postoperative corneal transplants.‖

The long-term administration of acetazoleamide has been reported from several clinics.¶ Statistics available from these independent sources are similar enough to be superimposed. It is quite clear that some patients with uncontrolled chronic simple glaucoma can be maintained normotensive for indefinite periods by the addition to their miotic regimen of approximately 250 mg. of acetazoleamide every six hours (or its equivalent in terms of delayed-action or long-acting preparations). Similar results may be obtained with a number of other carbonic anhydrase inhibitors. It must be emphasized that the effects of carbonic anhydrase inhibitors are reversible at any time, necessitating continuous around-the-clock medication.

In my experience, it has proved best to hospitalize patients for repeated tonography, tension curves, urinalysis and pH determination, blood pressure, and blood cell counts. In this fashion the best carbonic anhydrase inhibitor as well as its dose, frequency of administration, and side-effects can be determined for the individual patient. Adequate control of pressure was accomplished for prolonged periods of time in approximately two-thirds of patients with chronic simple glaucoma who responded initially to acetazoleamide. This occurred without apparent damage to cornea, retina, or lens and without progression of field loss. It is clear, however, that these patients must be followed very closely not only for progression of the outflow disorder (and rise of intraocular pressure in spite of effective partial suppression of secretion) but also for the appearance of side-effects. It has been the experience of many observers and repeatedly emphasized that miotic therapy should be continued when acetazoleamide therapy has been added to the regimen of patients with chronic simple glaucoma.

The side-effects have necessitated discontinuing this form of treatment in one-fourth to one-third of all patients where long-term therapy was attempted. Such side-effects have accounted for more than half of the failures of long-term acetazoleamide administration. On the other hand, poor control has been blamed for failure in only 10% to 15% of such cases. However, it should be noted that patients who failed to respond in satisfactory fashion to acetazoleamide initially were not included in most long-term series. The most prominent side-effects were paresthesias, but these were usually tolerated. Side-effects necessitating cessation of therapy have been inappetence and loss of weight, excessive fatigue, ureteral colic, and skin rashes.# In addition, hearing loss,* transient myopia,[80] thrombocytopenia,[501] agranulocytosis,[479] drug fever,[548] and a renal sulfonamide lesion[255] have been recorded. Side-effects were found to be more prominent in white and private populations of glaucoma patients than in Negro and clinic groups.[77] Most side-effects noted clinically to date have disappeared promptly on cessation of therapy, but there has been one report of a case of

‡ References 3, 80, 597, and 598.
§ References 574 and 575.
‖ Reference 476; Becker, B.: Unpublished data.
¶ References 77, 375, 393, and 605.
# References 77 and 393.
* Becker, B.: Unpublished data.

fatal bone marrow depression.[608] Some patients who could not tolerate acetazoleamide were maintained successfully on other carbonic anhydrase inhibitors.†

Dysuria and ureteral colic have been noted more frequently as side-effects since their recognition as conditions related to acetazoleamide administration.‡ It is of considerable interest that renal calcinosis can be produced in rats by the administration of acetazoleamide.[298] One of the first effects noted in these experimental animals following carbonic anhydrase inhibition was the profound fall in urinary citrate excretion. It was suggested that the decrease in citrate excretion following administration of acetazoleamide might explain the failure to keep calcium salts solubilized in the urine. Comparable measurements on human urinary citrate excretion have not been made, nor are there reports of the analysis of the ureteral calculi occurring in such patients. Therefore, it has not been determined whether the observed episodes of ureteral colic were based upon calcium deposits, sulfonamide crystals, or hematuria with blood clots. Reports on the use of salicylates in the therapy of recurrent renal calculi [33] suggest one means of possibly avoiding this complication of long-term acetazoleamide therapy. Such therapy is under study clinically on an experimental basis, but data are insufficient at this writing to recommend it as a routine procedure.

There is a need for effective carbonic anhydrase inhibitors which avoid some or all of the side-effects noted. Several laboratories and glaucoma clinics are directing their efforts towards this goal.

3. *Other Pharmacologic Agents That Induce Alterations in Rate of Secretion of Aqueous.*—(*a*) Vasopressin: The antidiuretic hormone, vasopressin (β-hypophamine), has been found to lower intraocular pressure in rabbits or patients.§ These findings have been confirmed by repeated tonography, and it has been demonstrated that the effective lowering of intraocular pressure following the topical administration of 1 unit of vasopressin results from a decreased production of aqueous humor.‖ Following topical application of vasopressin to normal or glaucomatous eyes, an average of 60% suppression of flow is recorded. Unfortunately, the drug is less effective in eyes subjected to miotic or acetazoleamide therapy. The rapid development of a state of resistance to the drug has limited its clinical use to short-term application. In rabbit eyes the compensatory decrease in facility of outflow, following some 60% depression of aqueous inflow, has again been demonstrated, much as after carbonic anhydrase inhibition.

The vasoconstrictive effects of vasopressin have been noted in dogs' eyes [146] and were documented recently in rabbit eyes.[664] The role played by such a decrease in blood supply to the ciliary body in the suppression of aqueous secretion has provided an interesting field for speculation and further experimental investigation. On the other hand, vasopressin has proved effective in changing the rate of water movement across the skin of the toad and the frog as well as across the mammalian renal tubules.[361] It has been suggested that this action of the antidiuretic hormone results from an increase in number or size of the pores of the membrane. The relationship of such membrane changes in the eye to secretion of aqueous humor remains obscure.

(*b*) Sympathomimetic Drugs: Epinephrine, phenylephrine (Neo-synephrine), hydroxyamphetamine (Paredine), naphazoline (Privine), and other related com-

† Becker, B.: Unpublished data.

‡ References 77 and 90; Becker, B.: Unpublished data.

§ References 219 and 538.

‖ References 68 and 149.

pounds have been noted to decrease intraocular pressure when applied topically to the eye.¶ The ability of epinephrine to decrease rate of flow of aqueous in human eyes has been noted in turnover studies with fluorescein.[258] However, it has been suggested that epinephrine and related vasconstrictive agents lower intraocular pressure by reducing the resistance to outflow offered by the sclera.[358] Tonographic data have demonstrated this not to be the mechanism of action of these agents. Rather, the decreased secretory rate was confirmed.#

Recently, the effects on the eye of epinephrine derivatives and related sympathomimetic amines have been investigated.[641] Inhibition of secretion was found not to require vasconstrictor activity. Thus, isoproterenol (Aludrine), which has minimal vasconstrictor activity, was demonstrated to lower intraocular pressure by decreasing the rate of aqueous flow. The mechanism of action of these drugs on the secretory process remains speculative. Unfortunately, no significant effects of these adrenergic compounds on composition or rate of flow of aqueous have been noted in animal eyes. These agents have proved useful clinically, however, for topical application in conjunction with miotic therapy in selected eyes with chronic simple or secondary glaucoma, but they have been contraindicated in closed angle glaucoma.*

(*c*) Adrenolytic Agents: Dibenamine (N,N-dibenzyl-β-chloroethylamine) has been demonstrated to lower intraocular pressure.† Suggestive evidence has been presented that the effect of this agent on animal eyes is to lower intraocular pressure by means of suppression of secretion.[176] A rise in anterior chamber bicarbonate and ascorbic acid has been observed five to six hours after Dibenamine administration to rabbits (in spite of a falling plasma ascorbate level).[297] The rise in ascorbic acid is qualitatively similar to that noted after acetazoleamide administration, but the elevation of anterior chamber bicarbonate after Dibenamine is quite the opposite of the effect of carbonic anhydrase inhibition. Thus, dibenamine appears to decrease inflow of water more than bicarbonate or ascorbic acid, resulting in rises in concentration of both of these substances. Unfortunately, posterior chamber data were not obtained on these animals. A slower turnover rate of glucose in the anterior chamber of treated rabbits was measured, which tended to confirm the depression of secretion by Dibenamine.[297] However, the hyperglycemia induced by the drug and the problems of glucose utilization in the eye make interpretation difficult. Furthermore, no changes were found in rate of accumulation of ascorbic acid in the anterior chamber in comparing Dibenamine-treated and control rabbits. This is difficult to explain and would appear to need reevaluation in terms of the current methods of analyzing turnover data.[352] A reexamination of the effects of Dibenamine on animal eyes, using repeated tonographic tracings, would be a simple and most enlightening experimental approach. Unfortunately, although the drug lowers intraocular pressure in human eyes, its toxicity and difficulty of administration limit its practical value.

Intravenous phenoxybenzamine (Dibenzyline), a sympatholytic agent related to Dibenamine, has been reported to lower intraocular pressure in three of six patients with acute glaucoma.[494] However, it raised intraocular pressure in three patients with chronic simple glaucoma. No significant lowering of intraocular

¶ References 75, 284, 294, 319, 627, and 641.
# References 75 and 640.
* References 202 and 491.
† References 102, 140, 144, 459, and 464.

pressure was found in glaucomatous eyes following oral administration of phenoxybenzamine. Furthermore, systemic toxicity was found to limit the use of this agent in the therapy of the glaucomas.

Phentolamine methanesulfonate (Regitine), an adrenolytic agent used in the diagnosis of pheochromocytoma,‡ has been found to lower intraocular pressure in rabbit eyes when applied topically or given systemically.§ Repeated tonographic tracings after 0.1 to 0.2 mg. revealed a fall in intraocular pressure and approximately 50% suppression of aqueous flow. A dose of 0.3 mg. resulted in a greater than 75% inhibition of flow at one and one-half to three hours, and this was accompanied by a fall in intraocular pressure as well as a decrease in outflow facility. [149] Attempts to lower intraocular pressure in normal or glaucomatous human eyes by means of local or systemic administration of Regitine have been unsuccessful.||

The adrenolytic ergot alkaloids have been reported to lower intraocular pressure temporarily in glaucomatous eyes.¶ Similar brief lowering of intraocular pressure has been produced by topical (6-acetoxythymyloxyethyl) dimethylamine (Opilon).[474]

On the other hand, local administration of tolazoline (Priscoline) or butyl sympatol (Vasculat) has been proposed as a means of provoking rises in intraocular pressure.# Suggestive tonographic evidence has been presented to indicate that this effect is induced by an increase in rate of aqueous production.*

The effects of adrenolytic agents on aqueous flow in rabbit eyes are of considerable interest when considered in association with the similar results noted following ganglionic blocking agents, chlorpromazine, and cervical sympathectomy in this species.

(*d*) Ganglionic Blocking Agents: The systemic administration of tetraethylammonium, hexamethonium, or pentolinium has been demonstrated to produce variable temporary falls in intraocular pressure in excess of the fall in blood pressure in rabbit or human eyes.† Tonographic tracings have demonstrated that this decrease in intraocular pressure appears to result from a temporary reversible decrease in formation of aqueous humor.‡ Furthermore, pentolinium decreased the diurnal fluctuations in intraocular pressure in some patients § and delayed the recovery of intraocular pressure following compression.[323] Similar blunting of diurnal changes in aqueous secretion has been noted following stellate ganglion block.[155] Because of bothersome systemic side-effects and failure to

‡ References 563 and 631.

§ Demorest, B. H., and Becker, B.: Unpublished data.

|| Becker, B.: Unpublished data.

¶ References 1, 459, 487, 555, 593, and 594.

References 398 and 401.

* References 371 and 583.

† References 53, 126, 184, 195, 325, 417, 520, and 535. Rosen, D. A.: The Effects of a Ganglionic Blocking Drug, Pentapyrrolidinium, on Ocular Fluid Dynamics: A Preliminary Report, read before the East Central Section of the Association for Research in Ophthalmology, Toronto, Canada, Jan. 9, 1954.

‡ Reference 184; Rosen, D. A.: The Effects of a Ganglionic Blocking Drug, Pentapyrrolidinium, on Ocular Fluid Dynamics: A Preliminary Report, read before the East Central Section of the Association for Research in Ophthalmology, Toronto, Canada, Jan. 9, 1954.

§ Rosen, D. A.: The Effects of a Ganglionic Blocking Drug, Pentapyrrolidinium, on Ocular Fluid Dynamics: A Preliminary Report, read before the East Central Section of the Association for Research in Ophthalmology, Toronto, Canada, Jan. 9, 1954.

lower intraocular pressure when applied locally or injected retrobulbarly,[184] these agents have been of limited usefulness in the therapy of the glaucomas. Furthermore, permanent bilateral blindness has been described following the use of hexamethonium.[117]

(*e*) Retrobulbar Anesthesia: Retrobulbar injections of procaine and epinephrine have been known to lower intraocular pressure in glaucomatous and normal human eyes.[248] Repeated tonography has suggested an inhibition of secretion of aqueous as the mechanism of action of this procedure for the lowering of intraocular pressure.[182] It is of interest that a temporary rise in intraocular pressure in rabbits under urethan anesthesia was described following retrobulbar procaine or lidocaine (Xylocaine) injections.[276] The increase in intraocular pressure could be prevented by cervical sympathectomy (two rabbits) or Dibenamine administration (one rabbit).

(*f*) Chlorpromazine: Chlorpromazine, a tranquilizing agent, when administered systemically to rabbits in doses of 0.3 to 0.5 mg/kg., causes a profound decrease in aqueous secretion and intraocular pressure.[149] Topical administration has been found to be ineffective, however. Similar effects on intraocular pressure have been recorded in rabbit as well as cat eyes, with use of much larger doses (25 to 100 mg.).[478]

Following the administration of chlorpromazine to patients, decreases in vasomotor tone and systemic hypotension have been noted, demonstrating the sympatholytic effects of this drug.‖ Furthermore, a decrease in renal blood flow and glomerular filtration has been reported recently following intravenous chlorpromazine administration to patients.[473] In addition, a decrease in urinary excretion of antidiuretic hormone was noted following such injections. Chlorpromazine has been found to lower intraocular pressure in human eyes.¶ The use of this and other tranquilizing agents in the therapy of the glaucomas has also been reported.# However, the short-term oral or intramuscular administration of chlorpromazine to patients has failed to induce consistent alterations in aqueous flow or intraocular pressure in my experience.

(*g*) Cyanin and Styrylquinoline Dyes: The injection of toxic dyes into the carotid arteries of the rabbit has interfered with oxidative phosphorylation in the ciliary body and has resulted in a decrease in secretion of aqueous on the homolateral side. Evidence for this thesis has been presented in a series of papers.* Thus, these dyes were found to produce edema of the ciliary processes, to decrease their oxygen uptake, to lower intraocular pressure, and to reduce the ascorbate and bicarbonate content of the aqueous humor of the affected eye.

(*h*) Radiomimetic Agents: Following x-irradiation of the rabbit eye or systemic administration of iodoacetate, there is a temporary decrease in aqueous humor formation.† This accounts in large part for the ocular hypotony described.‡ It is not clear as to whether these are direct effects of irradiation upon the ciliary processes or secondary to the inflammatory reaction induced.

(*i*) Osmotic Factors: The lowering of intraocular pressure which follows the intravenous injection of sorbitol [82] has been demonstrated to be a consequence

‖ References 217 and 457.
¶ References 467 and 468.
# References 95, 265, 397, 509, and 623.
* References 37 and 38.
† References 74 and 141.
‡ Brown, D. V.: Personal communication to the author.

of a decrease in rate of aqueous flow.[180] Consumption of water, on the other hand, has resulted in an increase in the rate of aqueous flow in some eyes.§ These findings could be explained on the basis of the thesis of a dependence of rate of flow upon osmotic excess of the aqueous humor as compared with the plasma.[346]

(*j*) Phosphorylcholine: The local application of this agent has been proposed as a means of raising intraocular pressure for several days in rabbit and human eyes.[324] This important suggestion for the therapy of ocular hypotony needs confirmation. Tonography data would be of considerable interest before and after such therapy in order to learn the mechanism of its action. The clinical need[174] for therapeutic means of increasing aqueous secretion and raising intraocular pressure in some eyes, as well as curiosity about their effects on tonography and composition of the aqueous humor, should provide adequate stimuli for the discovery and study of such agents.

4. *Surgical Means of Changing Rate of Flow.*—(*a*) Carotid Ligation: The effects of unilateral carotid ligation in rabbits have been demonstrated to result in a 30% to 50% decrease in aqueous flow on the homolateral side.[365] A similar temporary decrease in aqueous secretion after carotid ligation has been noted in human eyes.[639] The decreased rate of secretion in rabbit eyes is partially compensated by a decrease in facility of outflow. Thus, a lesser fall in intraocular pressure is induced by the procedure. These tonographic findings have been confirmed in rabbit eyes by the observation of an increase in fluorescein appearance time on the side operated on as well as by the alteration in steady-state concentration of ascorbic acid in posterior chamber and anterior chamber aqueous humor.

The finding of an increase in anterior chamber lactate concentration[388] is also consistent with the decrease in rate of aqueous flow. However, no alteration in anterior chamber chloride and a small rise in anterior chamber bicarbonate was measured when comparison was made of homolateral and contralateral eyes following carotid occlusion.[506] It was concluded, therefore, that carotid occlusion did not alter aqueous flow. Unfortunately, posterior chamber chloride and bicarbonate data were not reported, which makes difficult the interpretation of these findings and their reconciliation with tonographic, fluorescein-appearance-time, and ascorbate data.

The concentration of ascorbic acid in the anterior chamber at plasma levels below saturation has previously been suggested and utilized as a measure of plasma flow through the ciliary processes.[409] Thus, carotid ligation was found to decrease anterior chamber ascorbic acid concentrations on the ligated side by some 20% when compared with the unligated side. These results were confirmed recently.[379] As Linnér pointed out, however, the interpretation of such anterior chamber concentration changes depends upon either assuming no variation in rate of aqueous secretion or correcting for changes induced by the procedure. The finding of a decreased rate of flow following carotid ligation would permit more time for diffusional loss of ascorbic acid from the anterior chamber and thus would lower anterior chamber concentrations. Under these circumstances, the anterior chamber concentration alone could not be utilized as a means of determining ciliary body blood flow. The finding of no significant difference between ligated and normal sides in posterior chamber concentrations of ascorbic

§ References 181, 532, 579, and 583.

acid || suggests that the availability of ascorbic acid from the plasma has been decreased to the same extent as the decrease in rate of secretion.[365] Thus, under these circumstances, the decrease in aqueous flow is a measure of the change in plasma flow through the ciliary processes. Posterior chamber ascorbate and lactate data are needed at elevated plasma ascorbic levels in order to interpret the mechanism of equalization of concentrations of these anions in the anterior chamber of ligated and unligated sides.¶ At any rate, it is apparent that posterior chamber measurements as well as estimates of aqueous flow must be taken into consideration before alterations in anterior chamber concentrations of ascorbic acid can be related to the rate of plasma flow through the ciliary processes.

(*b*) Cervical Sympathectomy: The removal of the superior cervical sympathetic chain in rabbits produces a profound fall in intraocular pressure on the operated-on side lasting 24 hours.[415] This occurs without affecting episcleral venous pressure or outflow facility and so must be assumed to depend upon secretory failure. These findings may be related to the similar effects of adrenolytic and ganglionic blocking agents discussed above. An increased permeability to fluorescein for 24 hours has been noted on the sympathectomized size.[374] It is of interest that merely cutting the preganglionic sympathetic chain fails to alter intraocular pressure in rabbits.# Unfortunately, cervical sympathectomy has proved of little or no permanent value in the therapy of the glaucomas.*

(*c*) Cyclodiathermy, Cycloelectrolysis, and Cycloanematization: These procedures have been recommended as surgical means for reducing intraocular pressure by damaging the ciliary body.† There is abundant tonographic evidence accumulated to suggest that aqueous flow has been reduced by these procedures.‡ A fall in anterior aqueous ascorbate and bicarbonate concentrations has been noted following experimental coagulation of the ciliary body.§ Such anterior chamber data are consistent with a decreased rate of aqueous flow, but they do not rule out alterations in secretion and diffusional exchange of these anions following coagulation. Various techniques have been described and favorable results have been reported from several clinics. Other observers have not been as enthusiastic about these procedures and have used them only as a last resort in hopelessly lost eyes.||

(*d*) Other Surgical Procedures: A number of operations upon the eye, including those designed to improve aqueous outflow, are frequently followed by a variable decrease in rate of formation of aqueous humor. This may account for much of the confusion that has arisen in attempting to correlate gonioscopic appearance after filtering procedures with intraocular pressure.[609] Thus, even following cataract extraction, a period of hypotony has been noted.¶ That periods of hyposecretion generally follow most other procedures on the anterior segment has been demonstrated by tonography as well as by fluorescein turnover studies.#

|| Becker, B.: Unpublished data.

¶ References 383, 409, and 506.

References 415 and 481.

* References 1, 327, and 447.

† References 4, 16, 56, 86-88, 92, 96, 119, 131, 134, 152, 158, 206, 215, 264, 283, 304, 360, 434, 477, 534, 542, 557, 625, 634, 635, and 658. Friedenwald, J. S.: Unpublished data.

‡ References 75, 268, 534, 614, 640, 647, and 649.

§ References 185 and 186.

|| References 152, 179, 376, and 436.

¶ References 203, 308, and 640. Becker, B.: Unpublished data.

References 75, 175, 258, 259, 370, and 640.

Cyclodialysis is one of the outstanding examples of a procedure that has been followed frequently by a profound and prolonged depression of secretion of aqueous humor that persisted and hypotonized the eye, even when the cleft had scarred over and outflow was again obstructed. Such conclusions can be criticized on the basis that tonography can only be used with reservations as a measure of aqueous flow when the episcleral venous pressure factor in outflow loses significance or means of measurement. This occurs in all filtering procedures into the subconjunctival or suprachoroidal spaces. However, the fluorometric findings of decreased aqueous flow and stagnation of aqueous following iridectomy, anterior sclerectomy, and cyclodialysis are not subject to this criticism.* Secretory suppression following various surgical maneuvers would appear to provide an explanation for a variable part of the pressure-lowering effects obtained. The degree and duration of the decreased flow as well as the immediate and long-term changes induced in outflow facility need careful evaluation in each glaucomatous eye. The correlation of such alterations with the ultimate functional results of the surgical procedure would prove most helpful, not only for estimating individual prognosis but also for choosing the most suitable operations.

III. Episcleral Venous Pressure (P_v)

It is evident from Equation (1) that variations in episcleral venous pressure can alter intraocular pressure. The clinical occurrence of significant changes in episcleral venous pressure is believed to be very unusual by most observers. However, a case of glaucoma associated with a mediastinal tumor and venous engorgement of the head has been reported.[78] Furthermore, unilateral glaucoma following a carotid cavernous fistula has been observed.[580] Such a patient has been studied and found to demonstrate normal tonographic values for outflow facility but an elevated episcleral venous pressure.[638] Recently, a second case has been documented, with an analysis of the beneficial effects of carotid ligation on the ocular hypertension.[639]

A higher systemic venous pressure in glaucomatous patients than in a comparable normal group has been recorded.[105] Glaucomatous subjects have been noted to have a higher systemic venous pressure in the morning, and this is believed to be an explanation for the diurnal curve of intraocular pressure.[650]

Several competent observers have published data which indicate that alterations of pressure in episcleral veins precede and play a causative role in some of the variations of intraocular pressure, such as the diurnal fluctuations.† Furthermore, changes in episcleral venous pressure are believed by these observers to explain some of the pressure changes of glaucoma as well as the effects of miotics. By means of serial photographs periodic constrictions of the anterior ciliary arteries were recorded, and they are believed to precede the venous changes noted.‡ Physiological constrictions have also been postulated at the exit points of the venous channels from the eye.[584]

The vasodilating effects of various topically applied miotics on the appearance of aqueous veins and episcleral vessels have been restudied by means of anterior chamber dye injections.§ Dilatation of these vessels has been observed associated

* References 258, 259, and 370.
† References 21-23, 32, 188, 201, 599, and 600.
‡ References 188 and 355.
§ References 404 and 405.

with the fall in intraocular pressure following inhalation of amyl nitrate in patients with chronic simple glaucoma.[154]

However, cause and effect are difficult to unravel in studies of variations in episcleral vessels. Thus, changes in episcleral venous pressure may be directly reflected in their effects upon intraocular pressure and perhaps facility of outflow. On the other hand, alterations in outflow facility or in aqueous secretion may change the appearance of episcleral vessels without necessarily resulting from such variations. For example, pilocarpine usually improves outflow facility, and this has been accepted as its mechanism of lowering intraocular pressure by most observers. In so doing, it may increase the size of aqueous veins for the period of time that the pressure is falling. On the other hand, if pilocarpine administration does lower episcleral venous pressure primarily, then this would be reflected in a fall of intraocular pressure (see Equation [2] above). However, following pilocarpine, a dilatation of iris as well as episcleral vessels may be seen, and this may result in increased permeability to fluorescein. Under these circumstances, pilocarpine has been noted to decrease the rate of secretion of aqueous. This partial secretory failure may be a consequence of a similarly increased permeability in the ciliary body, resulting in a leaky barrier for the pump mechanism.‖ Thus, the appearances of episcleral vessels alone are difficult to predict or interpret in terms of aqueous humor dynamics. There is need for additional simultaneous tonographic measurements as well as permeability and turnover studies on the same eyes.

It is most important to realize, however, that several investigators, using essentially the same techniques of examination, have not noted these significant changes in episcleral veins in normal or glaucomatous eyes.¶ Thus, in most eyes with chronic simple glaucoma and elevated intraocular pressure, episcleral venous pressure has been found to be either normal or below normal by these observers.[421]

It has been demonstrated in human eyes that topical pilocarpine or eserine as well as systemic acetazoleamide administration fails to alter episcleral venous pressure.[414] Carotid occlusion or cervical sympathectomy in rabbit eyes likewise has not changed significantly the pressure in episcleral veins. Kleinert # has confirmed the finding that acetazoleamide does not alter the appearance of aqueous veins in normal or glaucomatous human eyes. From these observations, however, he postulated that acetazoleamide improves the outflow facility rather than suppresses aqueous secretion. This conclusion is difficult to reconcile with tonographic data and studies of aqueous humor dynamics.

The question has been raised of the effects on episcleral venous pressure of the application of the weight of a tonometer.[75] This was suggested as a possible source of error in tonography, requiring suitable correction. Episcleral venous pressure has been measured during tonography and found to increase an average of only 1.25 mm. Hg.[413] This correction factor is now being applied routinely in the interpretation of tonograms in several laboratories.

It is clear that, in spite of much work to date, episcleral venous pressure as a factor of practical importance in the maintenance and alteration of intraocular pressure still remains an open question requiring further study.

‖ References 60 and 238.

¶ References 258, 262, 410, 413, 416, and 644.

References 354 and 357.

IV. Miscellaneous Glaucoma Topics

A. Reviews

The historical aspects of glaucoma and an excellent summary of present knowledge of this group of disorders have been published.* A symposium on aqueous flow and a conference on various aspects of glaucoma have provided authoritative and thought-provoking discussions of current concepts and recent advances in this field.† The glaucoma symposium held in Buffalo covered several clinical aspects of the subject.‡ At the meeting of the American Academy of Ophthalmology and Otolaryngology, a panel of outstanding experts presented a summary of present knowledge concerning congenital glaucoma, its pathology, occurrence, diagnosis, therapy, and prognosis.§ Emphasis was placed on early diagnosis and prompt goniotomy. There has appeared a survey of various methods of gonioscopy,|| as well as a monograph presenting much of the subject matter of this method of examination in a well-illustrated and most commendable fashion.¶

The influences of pharmacological agents on intraocular pressure have been reviewed in a most comprehensive manner.[269] The present state of knowledge about carbonic anhydrase inhibitors and their effects on respiration has been summarized, together with an analysis of the data on the role of this enzyme in secretion of urine, aqueous humor, cerebrospinal fluid, pancreatic juice, gastric hydrochloric acid, saliva, etc.[93] The symposium on ocular aspects of carbonic anhydrase inhibition,# as well as the classic pharmacologic studies of Maren* and the review of Berliner and Orloff,[93] are recommended reading for all interested in the basic pharmacology and postulated mechanisms for the action of carbonic anhydrase inhibitors.

B. Genetics

Genetic factors in closed angle glaucoma and depth of anterior chamber have been studied.† The siblings and children of 49 patients with acute glaucoma were found to have a statistically significant shallowing of the anterior chamber for their age. These findings have been confirmed recently, as well as the finding of a 4% incidence of unsuspected glaucoma in the relatives of patients with chronic simple glaucoma.[340] An additional 5.5% of such relatives were classified as having borderline glaucoma. A pedigree illustrating dominant inheritance of chronic simple glaucoma was reported with comments upon the usefulness of a family history in early detection of glaucoma.[300] It would appear that the relatives of glaucoma patients should provide a fertile field for glaucoma detection. Furthermore, in a survey of the relatives of glaucoma patients, an increased resistance to outflow of aqueous has been found to precede the rise in intraocular

* References 615 and 616.
† References 200 and 235.
‡ References 28, 249, 271, 334, 342, 360, 363, and 490.
§ References 49, 289, 444, 531, and 553.
|| References 552 and 554.
¶ References 221 and 222.
# Symposium: Recent Trends in Diamox Research, *Am. J. Ophth.* 40:129-155 (Nov., Pt. II) 1955.
* References 431 and 433.
† References 602 and 603.

pressure. This knowledge can be put to good use in conjunction with mass surveys for glaucoma by tonometry or multiple pattern visual field testing.‡

C. Tonometry

The decennial report of the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology [241] and the exhibit at the International Congress have aroused considerable interest in calibration and standardization of tonometers in European clinics.§

The frequency distribution of intraocular pressure in the normal population has been studied.‖ Measurements made with a Schiøtz tonometer, using the 1954 scale of Friedenwald, led to average values with a 5.5 gm. weight of approximately 16 mm. Hg. These agreed well with estimates obtained by Goldmann,[261] using his new aplanation tonometer. However, measurements with a 10 gm. weight were found to give higher values when the 1954 scale was used. Similar observations in a number of clinics have suggested that the 1954 scale needs revision.[240]

The sterilization of tonometers by ultraviolet light or flaming has been discussed.¶ A new electronic tonometer has been developed,[578] and a method for simplifying the measurement of scleral rigidity has been presented.[426]

A survey of 1000 hospital patients over 40 years of age for glaucoma, by means of tonometric measurements, led to the discovery of 19 unsuspected cases.[620] This finding agrees well with the results of mass tonometric screening, that some 2% of the population over 40 years of age have undetected glaucoma.# An incidence of primary glaucoma of 4.6% was reported in a series of 600 patients over 64 years of age.[366] Such data emphasize the value of routine tonometry in all medical examinations.* Not only must tonometry be taught and emphasized to all students but ophthalmologists must set the example by carrying out tonometry on all patients, regardless of diagnosis or tactile tension.† With the aid of accurate tonometry, rapid visual field testing, knowledge of age and familial aspects of the disease, and methods for earlier detection of the outflow disorder, there is an enormous need for further and more extensive mass surveys and case-finding studies. Only by such means can this surreptitious disease process, which becomes of increasing significance in an aging population, be discovered early and treated most effectively.

Finally, a large number of pertinent papers have appeared since last year's review [290] which are of interest to the glaucoma problem. These have not been referred to directly in this review, but every effort has been made to include them in the bibliography.‡ The failure to review these is not intended in any way to reflect upon the merits of these contributions.

640 Kingshighway (10).

‡ References 214 and 296.

§ References 5, 6, 263, 307, and 326.

‖ References 466 and 637.

¶ References 194 and 517.

References 112, 118, 663, and 667.

* References 218, 286, and 667.

† References 309 and 484.

‡ References 10-12, 17, 18, 31, 54, 81, 83, 97, 101, 103, 104, 113, 122-124, 128, 130, 147, 148, 151, 153, 156, 157, 169, 172, 178, 189, 190, 196-198, 205, 212, 220, 223, 230, 232, 244, 246, 247, 282, 293, 299, 315, 317, 318, 328, 331, 333, 335, 337, 339, 343, 359, 364, 373, 385, 390, 396, 399, 403, 407, 419, 437, 439, 440, 442, 448, 452, 453, 462, 465, 470, 472, 480, 488, 489, 499, 500, 502, 514, 516, 518, 519, 525-527, 530, 536, 544, 545, 559, 562, 577, 581, 582, 585, 601, 604, 610, 618, 619, 648, 655, 659, 665, and 666.

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News and Comment

PERSONAL

Dr. William John Holmes.—Dr. William John Holmes, of Honolulu, has recently returned from a trip to the Orient and Australia. In Japan, Korea, and Okinawa, Dr. Holmes served as ophthalmologic consultant to the Office of Civil Affairs and Military Government, Department of Army. In Australia and New Zealand, along with Prof. Jules François, he was guest of honor at the annual Australian Ophthalmological Society, in Brisbane, and the annual meeting of the New Zealand Ophthalmological Society, in Wellington. He was made honorary member of both of these societies.

Dr. John McGavic.—The appointment of Dr. John S. McGavic as professor of ophthalmology, Temple-University Medical Center, has been announced by Dr. Glen Gregory Gibson, professor and head of the department.

Dr. McGavic recently resigned his post as pathologist and chief of laboratories at the Wills Eye Hospital.

He is also professor of clinical ophthalmology at the University of Pennsylvania Graduate School of Medicine and is in charge of the eye service at the Bryn Mawr Hospital.

Dr. Erling W. Hansen Honored.—Dr. Erling W. Hansen, Professor of Ophthalmology at the University of Minnesota Medical School, was honored by a testimonial dinner given by 82 of his colleagues on Sept. 19 at the Town and Country Club, St. Paul, Minn., celebrating his election to the presidency of the American Academy of Ophthalmology and Otolaryngology.

ANNOUNCEMENTS

New York University Post-Graduate Medical School Course.—Surgery of the Cornea will be offered as a full-time course by the New York University Post-Graduate Medical School from Dec. 3 through 7.

Given under the direction of Dr. Ramon Castroviejo, the course is designed to cover thoroughly the current concepts and practices in the field of corneal surgery by means of lectures, observation of surgical procedures in the operating room, and practice on animal eyes.

Surgery of the Cornea is one of 11 courses offered by the Post-Graduate Department of Ophthalmology during the academic year. For further information, write to the Dean, Post-Graduate Medical School, 550 First Ave., New York 16.

Books

Blur of the Retinal Image. By Glenn A. Fry, M.D. Price, 3.50. Pp. 120. The Ohio State University Press, Columbus, Ohio, 1955.

This small book is a fairly technical discussion of how the distribution of the intensity of light within the retinal image can be determined. The first-order effects and roles played by out-of-focus images, diffraction, axial chromatic aberration, chromatic dispersion, small astigmatism, spherical aberration, and pupil size in this distribution are developed analytically. The consideration deals with point sources of light, the straight line boundary between light and dark areas, and luminous line objects. It is assumed at the outset that the simple distribution of light within the image can be described by the normal error-distribution curve. From this as a basis an "index of blur" is defined. Much of the book then is concerned with determining the variation of this index under the influence of the different factors listed above. The discussion of the characteristics of the retinal image due to diffraction alone in out-of-focus images is particularly interesting. Similarly, the chapter on the relative roles played by diffraction and spherical aberration on the out-of-focus images is enlightening. According to the calculations, the eye with spherical aberration is nearly equivalent to an eye free from spherical aberration, if one considers the point of best focus to lie about 0.26 mm. in front of the paraxial focus, which is equivalent to 0.72 D. The caustic surface appears unrelated to the concentration of light in the image.

The author summarizes by stating as follows: "It is believed that the calculations presented herein have sufficiently demonstrated that simple blur circle theory gives an approximation to the truth, even in the case of spherical aberration, which completely justifies the classical use to which it has been put in dealing with accommodation and refraction, and justifies the effort which is generally made by refractionists to work within a precision of an eighth to a quarter of a diopter." The analysis presented is deemed needed in investigations of perception of fine detail. The reviewer is certain also that the author would be the first to admit that generally the analysis is only a first approximation to the case of the average eye, where the lack of axial symmetry of the refractive surfaces and the ever-present astigmatic irregularities of those surfaces tend to complete the distribution of light in out-of-focus images. One only needs to accommodate voluntarily while observing a luminous object against a black background (say, the moon at night) to see several separate higher concentrations of light. Apart from this criticism, Dr. Fry's book is a valuable contribution and it will provide a reference text for those concerned with the finer aspects of the problem of the retinal image.

The average reader without some background in optics and mathematics may find the book difficult to read. Probably there should have been more amplification of the discussion following the development of each topic.

The book is a photographic offset of typewritten material but is easily readable.

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INDEX TO A. M. A. ARCHIVES OF OPHTHALMOLOGY

FOR THE PERIOD

JULY THROUGH DECEMBER, 1956

AMERICAN MEDICAL ASSOCIATION Publication

THIS INDEX consists of two parts: Author and Title Index and Subject Index. A Table of Contents is not included, and subscribers who want one in the bound volume should arrange to have the Table of Contents of each of the six issues of this volume included among the pages to be bound.

AUTHOR AND TITLE INDEX TO VOLUME 56

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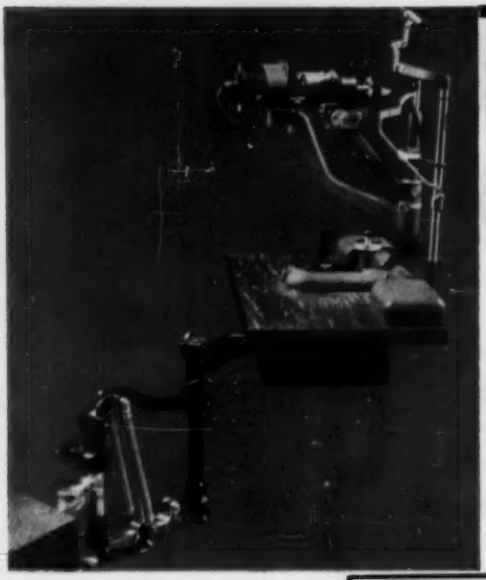

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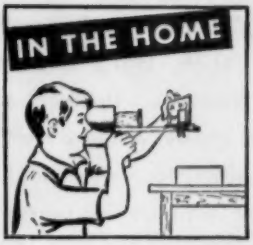

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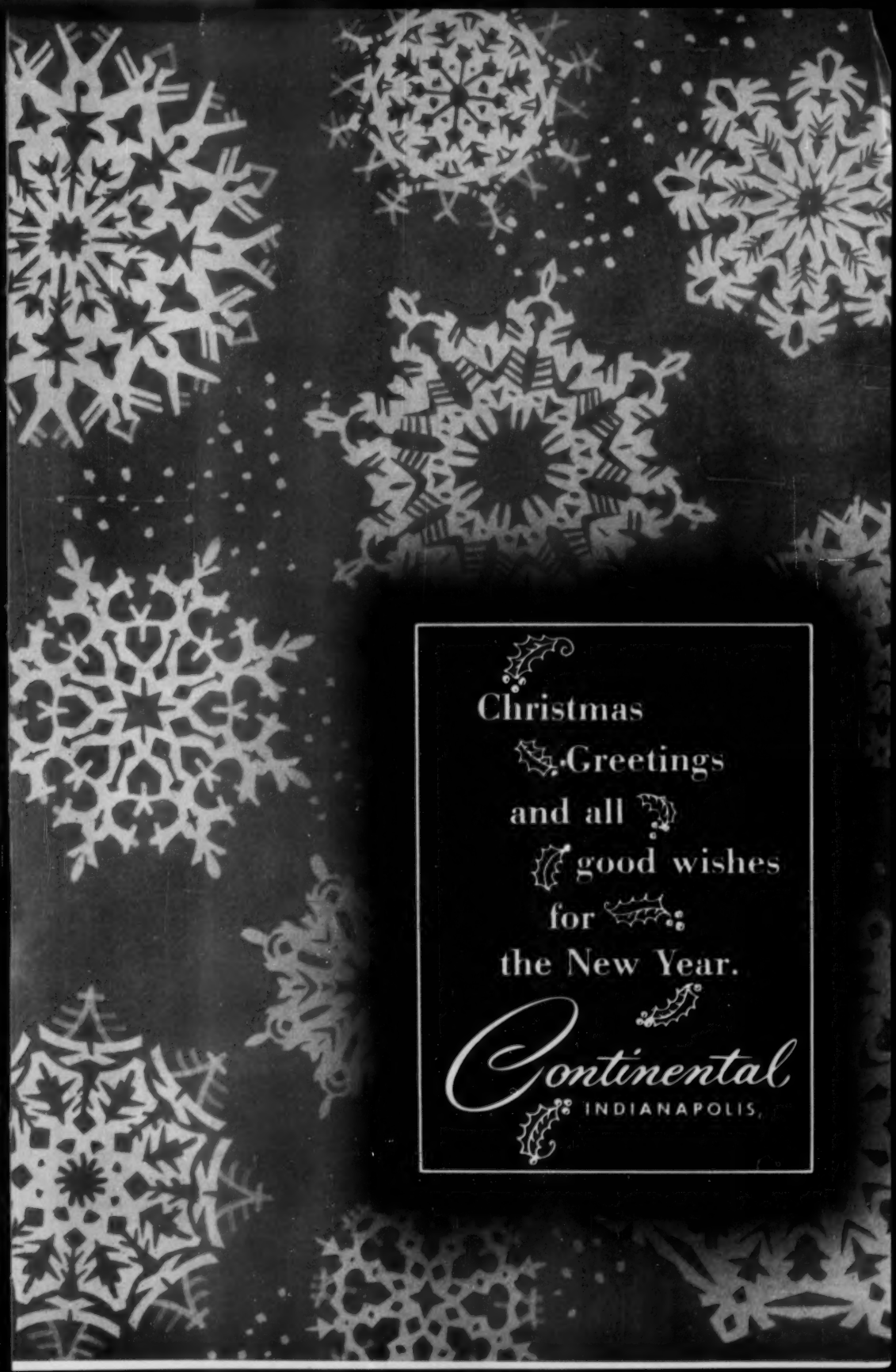
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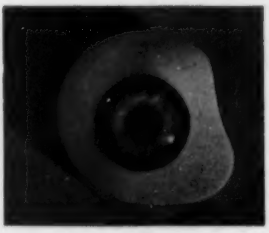

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*Schlegel, H. E., Jr., and Swan, K. C.: A. M. A. Arch. Ophth. *51*:643 (May) 1954.

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CASE HISTORY #1

The case history presented below demonstrates how Catarex Service helped the patient through the post-operative period with adequate vision.

The extreme ease with which Rx changes can be made with CATAREX T gives the patient, post-operatively, the best possible vision at all times until the operated eye has stabilized sufficiently for the final correction. And a permanent lens identical to the temporary style — CATAREX D — may be prescribed to carry through the ophthalmologist's work to its logical conclusion.

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CASE HISTORY – Mr. F. S.

Mr. F.S., a 55-year-old businessman, had been aware of a gradual and painless reduction of his visual acuity for more than a year. Examination revealed cataractous changes in each lens, particularly marked in the posterior subcapsular cortex. Corrected right vision = 6/200; corrected left vision = 20/80. As this vision did not permit him to carry on with his duties, a right intracapsular lens extraction was performed on February 18, 1955. Post-operative course was uneventful and the patient was discharged on February 25th.

3-18-55: Manifest O.D. +10.50Dsph ○ +0.50Dcyl. ax 165 = 20/20—; +2.75D add = Jg. 0.75 @ 12½". Rx Right: Manifest findings in CATAREX T (temporary style) straight-top bifocal. Left: lens to balance.

4-12-55: Right vision with above CATAREX T lens = 20/40+. Manifest O.D. +10.50Dsph. ○ +1.50Dcyl. ax 105 = 20/15+; +2.75D add = Jg. 0.75 @ 13". Patient was allowed to retain first CATAREX T lens until second pair was received with new Rx.

5-5-55: Right vision with 4-12-55 Rx = 20/20. Manifest O.D. +10.00Dsph. ○ +1.50Dcyl. ax 105 = 20/15+. Again, patient was allowed to retain former lens until the new Rx in CATAREX T was ready.

5-31-55: Right vision with 5-5-55 Rx = 20/50. Manifest O.D. +10.00Dsph. ○ +1.00Dcyl. ax 60 = 20/15+. Rx Right: Manifest findings in CATAREX T. Left: lens to balance.

7-6-55: Right vision with 5-31-55 Rx = 20/20+. Manifest O.D. +10.00Dsph. ○ +1.00Dcyl. ax 75 = 20/15+. Rx Right: Manifest findings in CATAREX T. Left: lens to balance.

7-27-55: Manifest O.D. +10.50Dsph. ○ +1.25Dcyl. ax 90 = 20/15+; +2.75D add = Jg. 0.75 @ 13¾". Rx Right: CATAREX D (permanent). Left: lens to balance.

1-18-56: With permanent CATAREX D lens, right vision = 20/15+; Jg. 0.75 at 13".

The patient, who secured his first CATAREX T (temporary) bifocal lens one month after surgery and had five different Rxes in temporary lenses, secured his first and only permanent lens, CATAREX D, approximately five months after surgery; to date he has not had to have it changed or re-surfaced. Thus, the maximum visual acuity of which the eye was capable was made available to the patient during the greater part of the post-operative period by frequent changes of CATAREX T lenses as indicated, and finally by the permanent CATAREX D lens. With this lens, the patient is most comfortable ocularly at his work and templates having his left cataract extracted in the near future.

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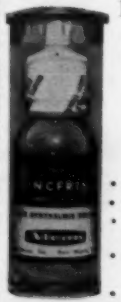

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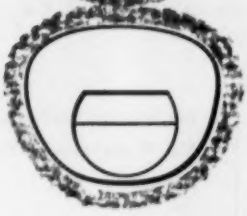

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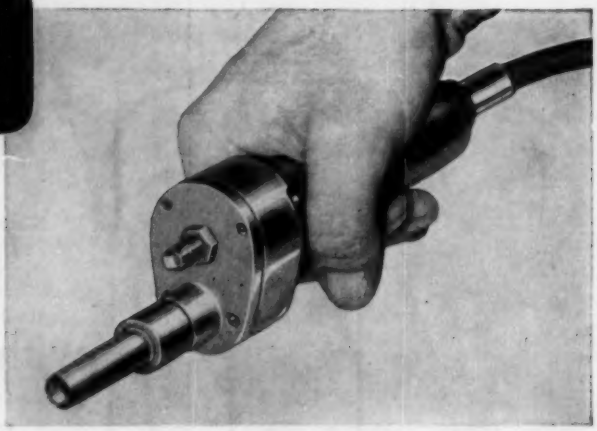

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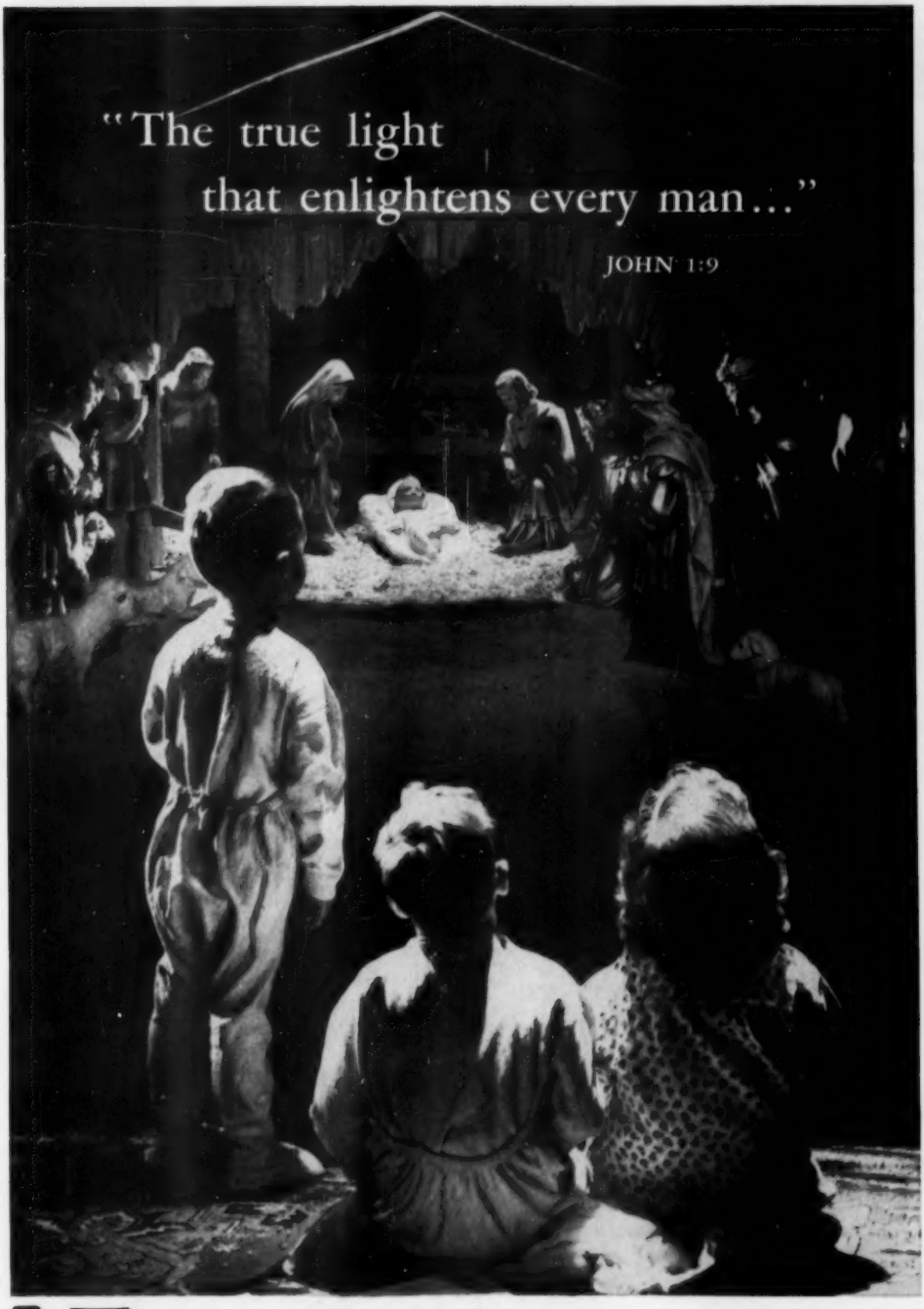

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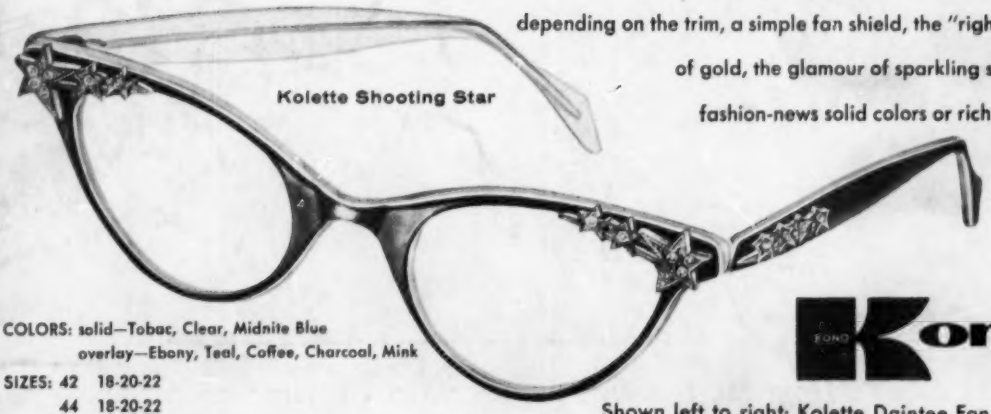

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